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OBG MANAGEMENT

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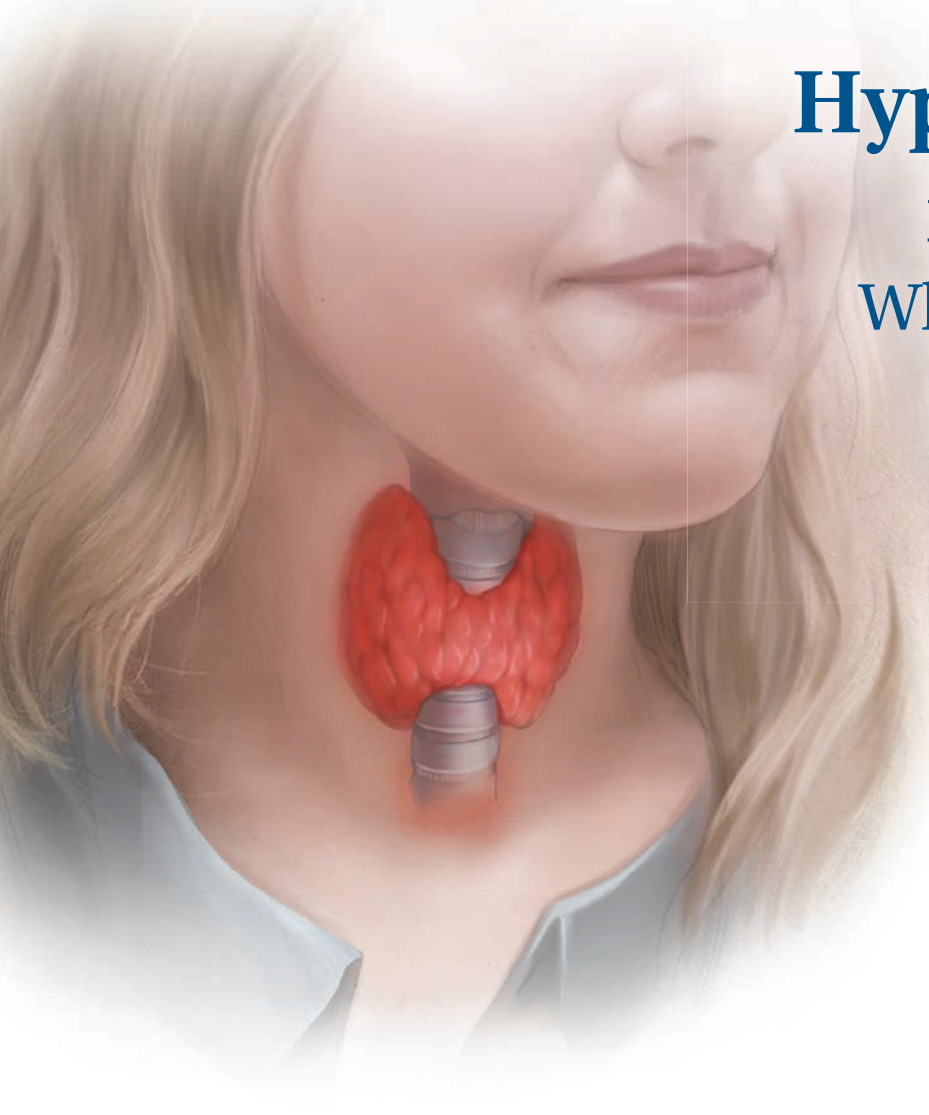

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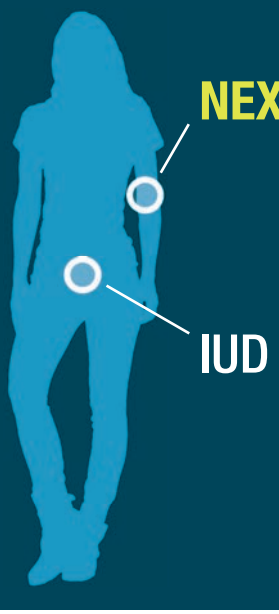

Help your patients understand both of their LARC location options[1]

IUD, intrauterine device; LARC, long-acting reversible contraceptive.

NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

- NEXPLANON should not be used in women who have known or suspected pregnancy; current or past history of thrombosis or thromboembolic disorders; liver tumors, benign or malignant, or active liver disease; undiagnosed abnormal genital bleeding; known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past; and/or allergic reaction to any of the components of NEXPLANON.

Complications of insertion and removal

- NEXPLANON should be inserted subdermally and be palpable after insertion. Palpate immediately after insertion to ensure proper placement. Undetected failure to insert the implant may lead to unintended pregnancy. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.
- Insertion and removal-related complications may include pain, paresthesias, bleeding, hematoma, scarring, or infection. If NEXPLANON is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur. Implant removal may be difficult or impossible if the implant is not inserted correctly, inserted too deeply, not palpable, encased in fibrous tissue, or has migrated. If at any time the implant cannot be palpated, it should be localized and removal is recommended.
- There have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. Endovascular or surgical procedures may be needed for removal.

NEXPLANON and pregnancy

- Be alert to the possibility of an ectopic pregnancy in women using NEXPLANON who become pregnant or complain of lower abdominal pain.
- **Rule out pregnancy before inserting NEXPLANON.**

Educate her about the risk of serious vascular events

- The use of combination hormonal contraceptives increases the risk of vascular events, including arterial events [stroke and myocardial infarction (MI)] or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis (DVT), retinal vein thrombosis, and pulmonary embolism). Women with risk factors known to increase the risk of these events should be carefully assessed. Postmarketing reports in women using etonogestrel implants have included pulmonary emboli (some fatal), DVT, MI, and stroke. NEXPLANON should be removed if thrombosis occurs.

US-XPL-00588 05/19

NEXPLANON is the only non-uterine LARC

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

Up to **3 years** of pregnancy prevention*

>99% effective†

Reversible if her plans change

Placed subdermally just under the skin in the inner upper arm

*NEXPLANON must be removed by the end of the third year and may be replaced by another NEXPLANON at the time of removal, if continued contraceptive protection is desired.

†Less than 1 pregnancy per 100 women who used NEXPLANON for 1 year.

(Actual implant shown; actual implant is 4 cm)

SELECTED SAFETY INFORMATION *(continued)*

- Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum.
- Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. Consider removing the NEXPLANON implant in case of long-term immobilization due to surgery or illness.

Counsel her about changes in bleeding patterns

- Women are likely to have changes in their menstrual bleeding pattern with NEXPLANON, including changes in frequency, intensity, or duration. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy. In clinical studies of the non-radiopaque etonogestrel implant, changes in bleeding pattern were the most common reason reported for stopping treatment (11.1%). Counsel women regarding potential changes they may experience.

Be aware of other serious complications, adverse reactions, and drug interactions

- Remove NEXPLANON if jaundice occurs.
- Remove NEXPLANON if blood pressure rises significantly and becomes uncontrolled.
- Prediabetic and diabetic women using NEXPLANON should be carefully monitored.
- Carefully observe women with a history of depressed mood. Consider removing NEXPLANON in patients who become significantly depressed.
- The most common adverse reactions (≥10%) reported in clinical trials were headache (24.9%), vaginitis (14.5%), weight increase (13.7%), acne (13.5%), breast pain (12.8%), abdominal pain (10.9%), and pharyngitis (10.5%).
- Drugs or herbal products that induce enzymes, including CYP3A4, may decrease the effectiveness of NEXPLANON or increase breakthrough bleeding.
- The efficacy of NEXPLANON in women weighing more than 130% of their ideal body weight has not been studied. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. Therefore, NEXPLANON may be less effective in overweight women.
- Counsel women to contact their health care provider immediately if, at any time, they are unable to palpate the implant.
- NEXPLANON does not protect against HIV or other STDs.

Please read the adjacent Brief Summary of the Prescribing Information.

Reference:

1. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 186: Long-acting reversible contraception: implants and intrauterine devices. *Obstet Gynecol.* 2017;130(5):e251–e269.

MERCK

Nexplanon®
(etonogestrel implant) 68mg

BRIEF SUMMARY (For full Prescribing Information, see package insert.)

Women should be informed that this product does not protect against HIV infection (the virus that causes AIDS) or other sexually transmitted diseases.

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

The efficacy of NEXPLANON does not depend on daily, weekly or monthly administration. All healthcare providers should receive instruction and training prior to performing insertion and/or removal of NEXPLANON. A single NEXPLANON implant is inserted subdermally just under the skin at the inner side of the non-dominant upper arm. The insertion site is overlying the triceps muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localization and/or removal can be difficult or impossible *[see Dosage and Administration and Warnings and Precautions]*. NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant must be removed by the end of the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

- Known or suspected pregnancy
- Current or past history of thrombosis or thromboembolic disorders
- Liver tumors, benign or malignant, or active liver disease
- Undiagnosed abnormal genital bleeding
- Known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past
- Allergic reaction to any of the components of NEXPLANON *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

The following information is based on experience with the etonogestrel implants (IMPLANON® [etonogestrel implant] and/or NEXPLANON), other progestin-only contraceptives, or experience with combination (estrogen plus progestin) oral contraceptives.

Complications of Insertion and Removal

NEXPLANON should be inserted subdermally so that it will be palpable after insertion, and this should be confirmed by palpation immediately after insertion. Failure to insert NEXPLANON properly may go unnoticed unless it is palpated immediately after insertion. Undetected failure to insert the implant may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesias, bleeding, hematoma, scarring or infection, may occur.

If NEXPLANON is inserted deeply (intramuscular or in the fascia), neural or vascular injury may occur. To help reduce the risk of neural or vascular injury, NEXPLANON should be inserted subdermally just under the skin at the inner side of the non-dominant upper arm overlying the triceps muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. Deep insertions of NEXPLANON have been associated with paraesthesia (due to neural injury), migration of the implant (due to intramuscular or fascial insertion), and intravascular insertion. If infection develops at the insertion site, start suitable treatment. If the infection persists, the implant should be removed. Incomplete insertions or infections may lead to expulsion.

Implant removal may be difficult or impossible if the implant is not inserted correctly, is inserted too deeply, not palpable, encased in fibrous tissue, or has migrated.

There have been reports of migration of the implant within the arm from the insertion site, which may be related to deep insertion. There also have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be needed for removal.

If at any time the implant cannot be palpated, it should be localized and removal is recommended.

Exploratory surgery without knowledge of the exact location of the implant is strongly discouraged. Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm. If the implant is located in the chest, healthcare providers familiar with the anatomy of the chest should be consulted. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.

Changes in Menstrual Bleeding Patterns

After starting NEXPLANON, women are likely to have a change from their normal menstrual bleeding pattern. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration. In clinical trials of the non-radiopaque etonogestrel implant (IMPLANON), bleeding patterns ranged from amenorrhea (1 in 5 women) to frequent and/or prolonged bleeding (1 in 5 women). The bleeding pattern experienced during the first three months of NEXPLANON use is broadly predictive of the future bleeding pattern for many women. Women should be counseled regarding the bleeding pattern changes they may experience so that they know what to expect. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy.

In clinical studies of the non-radiopaque etonogestrel implant, reports of changes in bleeding pattern were the most common reason for stopping treatment (11.1%). Irregular bleeding (10.8%) was the single most common reason women stopped treatment, while amenorrhea (0.3%) was cited less frequently. In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3,315 intervals of 90 days recorded by 780 patients). The percentages of patients having 0, 1-7, 8-21, or >21 days of spotting or bleeding over a 90-day interval while using the non-radiopaque etonogestrel implant are shown in Table 1.

Table 1: Percentages of Patients With 0, 1-7, 8-21, or >21 Days of Spotting or Bleeding Over a 90-Day Interval While Using the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Total Days of Spotting or Bleeding	Percentage of Patients		
	Treatment Days 91-180 (N = 745)	Treatment Days 271-360 (N = 657)	Treatment Days 631-720 (N = 547)
0 Days	19%	24%	17%
1-7 Days	15%	13%	12%
8-21 Days	30%	30%	37%
>21 Days	35%	33%	35%

Bleeding patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of 90-day intervals with these bleeding patterns, are summarized in Table 2.

Table 2: Bleeding Patterns Using the Non-Radiopaque Etonogestrel Implant (IMPLANON) During the First 2 Years of Use*

Bleeding Patterns	Definitions	%†
Infrequent	Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)	33.6
Amenorrhea	No bleeding and/or spotting in 90 days	22.2
Prolonged	Any bleeding and/or spotting episode lasting more than 14 days in 90 days	17.7
Frequent	More than 5 bleeding and/or spotting episodes in 90 days	6.7

* Based on 3315 recording periods of 90 days duration in 780 women, excluding the first 90 days after implant insertion

† % = Percentage of 90-day intervals with this pattern

In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy.

Ectopic Pregnancies

As with all progestin-only contraceptive products, be alert to the possibility of an ectopic pregnancy among women using NEXPLANON who become pregnant or complain of lower abdominal pain. Although ectopic pregnancies are uncommon among women using NEXPLANON, a pregnancy that occurs in a woman using NEXPLANON may be more likely to be ectopic than a pregnancy occurring in a woman using no contraception.

Thrombotic and Other Vascular Events

The use of combination hormonal contraceptives (progestin plus estrogen) increases the risk of vascular events, including arterial events (strokes and myocardial infarctions) or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism). NEXPLANON is a progestin-only contraceptive. It is unknown whether this increased risk is applicable to etonogestrel alone. It is recommended, however, that women with risk factors known to increase the risk of venous and arterial thromboembolism be carefully assessed. There have been postmarketing reports of serious arterial and venous thromboembolic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction, and strokes, in women using etonogestrel implants. NEXPLANON should be removed in the event of a thrombosis.

Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. Evaluate for retinal vein thrombosis immediately if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Consider removal of the NEXPLANON implant in case of long-term immobilization due to surgery or illness.

Ovarian Cysts

If follicular development occurs, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles disappear spontaneously. On rare occasion, surgery may be required.

Carcinoma of the Breast and Reproductive Organs

Women who currently have or have had breast cancer should not use hormonal contraception because breast cancer may be hormonally sensitive *[see Contraindications]*. Some studies suggest that the use of combination hormonal contraceptives might increase the incidence of breast cancer; however, other studies have not confirmed such findings. Some studies suggest that the use of combination hormonal contraceptives is associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors. Women with a family history of breast cancer or who develop breast nodules should be carefully monitored.

Liver Disease

Disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal. Remove NEXPLANON if jaundice develops. Hepatic adenomas are associated with combination hormonal contraceptives use. An estimate of the attributable risk is 3.3 cases per 100,000 for combination hormonal contraceptives users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON. The progestin in NEXPLANON may be poorly metabolized in women with liver impairment. Use of NEXPLANON in women with active liver disease or liver cancer is contraindicated *[see Contraindications]*.

Weight Gain

In clinical studies, mean weight gain in U.S. non-radiopaque etonogestrel implant (IMPLANON) users was 2.8 pounds after one year and 3.7 pounds after two years. How much of the weight gain was related to the non-radiopaque etonogestrel implant is unknown. In studies, 2.3% of the users reported weight gain as the reason for having the non-radiopaque etonogestrel implant removed.

Elevated Blood Pressure

Women with a history of hypertension-related diseases or renal disease should be discouraged from using hormonal contraception. For women with well-controlled hypertension, use of NEXPLANON can be considered. Women with hypertension using NEXPLANON should be closely monitored. If sustained hypertension develops during the use of NEXPLANON, or if a significant increase in blood pressure does not respond adequately to antihypertensive therapy, NEXPLANON should be removed.

Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among combination hormonal contraceptive users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

Carbohydrate and Lipid Metabolic Effects

Use of NEXPLANON may induce mild insulin resistance and small changes in glucose concentrations of unknown clinical significance. Carefully monitor prediabetic and diabetic women using NEXPLANON. Women who are being treated for hyperlipidemia should be followed closely if they elect to use NEXPLANON. Some progestins may elevate LDL levels and may render the control of hyperlipidemia more difficult.

Depressed Mood

Women with a history of depressed mood should be carefully observed. Consideration should be given to removing NEXPLANON in patients who become significantly depressed.

Return to Ovulation

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in blood decreased below sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.

Nexplanon®
(etonogestrel implant) 68mg

Fluid Retention
Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.

Contact Lenses
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

***In Situ* Broken or Bent Implant**
There have been reports of broken or bent implants while in the patient's arm. Based on *in vitro* data, when an implant is broken or bent, the release rate of etonogestrel may be slightly increased. When an implant is removed, it is important to remove it in its entirety *[see Dosage and Administration].*

Monitoring
A woman who is using NEXPLANON should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.

Drug-Laboratory Test Interactions
Sex hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

ADVERSE REACTIONS
In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON® [etonogestrel implant]) (11.1% of women).
Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 3.

Table 3: Adverse Reactions Leading to Discontinuation of Treatment in 1% or More of Subjects in Clinical Trials of the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Adverse Reactions	All Studies N = 942
Bleeding Irregularities*	11.1%
Emotional Lability†	2.3%
Weight Increase	2.3%
Headache	1.6%
Acne	1.3%
Depression‡	1.0%

*Includes "frequent", "heavy", "prolonged", "spotting", and other patterns of bleeding irregularity.
† Among US subjects (N=330), 6.1% experienced emotional lability that led to discontinuation.
‡ Among US subjects (N=330), 2.4% experienced depression that led to discontinuation.

Other adverse reactions that were reported by at least 5% of subjects in the non-radiopaque etonogestrel implant clinical trials are listed in Table 4.

Table 4: Common Adverse Reactions Reported by ≥5% of Subjects in Clinical Trials With the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Adverse Reactions	All Studies N = 942
Headache	24.9%
Vaginitis	14.5%
Weight increase	13.7%
Acne	13.5%
Breast pain	12.8%
Abdominal pain	10.9%
Pharyngitis	10.5%
Leukorrhea	9.6%
Influenza-like symptoms	7.6%
Dizziness	7.2%
Dysmenorrhea	7.2%
Back pain	6.8%
Emotional lability	6.5%
Nausea	6.4%
Pain	5.6%
Nervousness	5.6%
Depression	5.5%
Hypersensitivity	5.4%
Insertion site pain	5.2%

In a clinical trial of NEXPLANON, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3.3% of subjects. Additionally, hematoma (3.0%), bruising (2.0%), pain (1.0%), and swelling (0.7%) were reported.

Effects of Other Drugs on Hormonal Contraceptives
Substances decreasing the plasma concentrations of hormonal contraceptives (HCs) and potentially diminishing the efficacy of HCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of HCs and potentially diminish the effectiveness of HCs or increase breakthrough bleeding.
Some drugs or herbal products that may decrease the effectiveness of HCs include efavirenz, phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between HCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with HCs, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of HCs: Co-administration of certain HCs and strong or moderate CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase the serum concentrations of progestins, including etonogestrel.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of progestin have been noted in cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine, efavirenz] or increase [e.g., etravirene]). These changes may be clinically relevant in some cases. Consult the prescribing information of anti-viral and anti-retroviral concomitant medications to identify potential interactions.

Effects of Hormonal Contraceptives on Other Drugs
Hormonal contraceptives may affect the metabolism of other drugs. Consequently, plasma concentrations may either increase (for example, cyclosporine) or decrease (for example, lamotrigine). Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant *[see Contraindications].* Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse development outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses of 315 or 781 times the anticipated human dose (60 µg/day). NEXPLANON should be removed if maintaining a pregnancy.

Lactation
Risk Summary
Small amounts of contraceptive steroids and/or metabolites, including etonogestrel are present in human milk. No significant adverse effects have been observed in the production or quality of breast milk, or on the physical and psychomotor development of breastfed infants. Hormonal contraceptives, including etonogestrel, can reduce milk production in breastfeeding mothers.This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.

Pediatric Use
Safety and efficacy of NEXPLANON have been established in women of reproductive age. Safety and efficacy of NEXPLANON are expected to be the same for postpubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.

Geriatric Use
This product has not been studied in women over 65 years of age and is not indicated in this population.

Hepatic Impairment
No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. The use of NEXPLANON in women with active liver disease is contraindicated *[see Contraindications].*

Overweight Women
The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

OVERDOSAGE
Overdosage may result if more than one implant is inserted. In case of suspected overdose, the implant should be removed.

NONCLINICAL TOXICOLOGY
In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day (equal to approximately 1.8-3.6 times the systemic steady state exposure in women using NEXPLANON), no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in the *in vitro* Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the *in vivo* mouse micronucleus test. Fertility in rats returned after withdrawal from treatment.

PATIENT COUNSELING INFORMATION *See FDA-Approved Patient Labeling.*
- Counsel women about the insertion and removal procedure of the NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. A USER CARD and consent form are included in the packaging. Have the woman complete a consent form and retain it in your records. The USER CARD should be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have a record of the location of the implant in the upper arm and when it should be removed.
- Counsel women to contact their healthcare provider immediately if, at any time, they are unable to palpate the implant.
- Counsel women that NEXPLANON does not protect against HIV infection (AIDS) or other STDs.
- Counsel women that the use of NEXPLANON may be associated with changes in their normal menstrual bleeding patterns so that they know what to expect.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA.

For more detailed information, please read the Prescribing Information.
USPI-MK8415-IPTX-1810r020
Revised: 10/2018

MERCK

#1 IN READERSHIP*

OBG MANAGEMENT

mdedge.com/obgyn

Enhancing the quality of women's health care and the professional development of ObGyns and all women's health care clinicians†

*Source: Kantar Media, Medical Surgical Study June 2019, Obstetrics/Gynecology Combined Office & Hospital Readers.
†OBG MANAGEMENT recognizes the importance of addressing the reproductive health of gender-diverse individuals.

COLORECTAL CANCER (CRC) IS THE MOST PREVENTABLE, YET LEAST PREVENTED FORM OF CANCER.[1]

COLOGUARD® IS RECOMMENDED BY ACOG GUIDELINES^[2] AND HAS BEEN CLINICALLY SHOWN TO DETECT AND RULE OUT COLORECTAL CANCER.[3]

92%
SENSITIVITY IN DETECTING CRC STAGES I-IV*[3]

87%
SPECIFICITY OVERALL†[3]

99.94%
NEGATIVE PREDICTIVE VALUE
If a patient received a negative Cologuard test result, there was a 99.94% chance that there was no CRC‡[3]

TO HELP DETECT CRC, OFFER COLOGUARD AS A CHOICE TO SCREEN APPROPRIATE WOMEN AS SOON AS THEY ARE ELIGIBLE.

Indication and Important Risk Information:
Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC) or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 50 years or older, who are at typical average risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

Cologuard is not for high-risk individuals, including patients with a personal history of colorectal cancer and adenoma; have had a positive result from another colorectal cancer screening method within the last 6 months; have been diagnosed with a condition associated with high risk for colorectal cancer such as IBD, chronic ulcerative colitis, Crohn's disease; or have a family history of colorectal cancer, or certain hereditary syndromes

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Cologuard performance when used for repeat testing has not been evaluated or established. Rx only.

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*Cologuard sensitivity, per stage of cancer: I: 90% (n=29); II: 100% (n=21); III: 90% (n=10); IV: 75% (n=4).[3]

†Cologuard specificity: 87% overall specificity, excluding CRC and advanced adenomas, and including all nonadvanced adenomas, nonneoplastic findings, and negative results on colonoscopy. 90% specificity in participants with no lesions biopsied on colonoscopy.[3]

‡Negative predictive value (NPV) is defined as the probability that disease is absent in those with a negative result; it is highly dependent on the prevalence of the disease. NPV was derived from the patient population evaluated in the Imperiale et al publication.[3]

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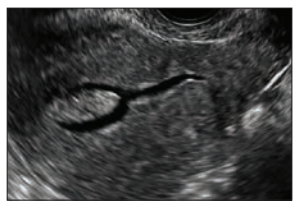

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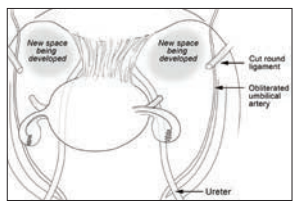

Hysterectomy in prior CD **38**

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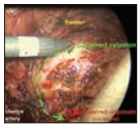

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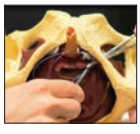

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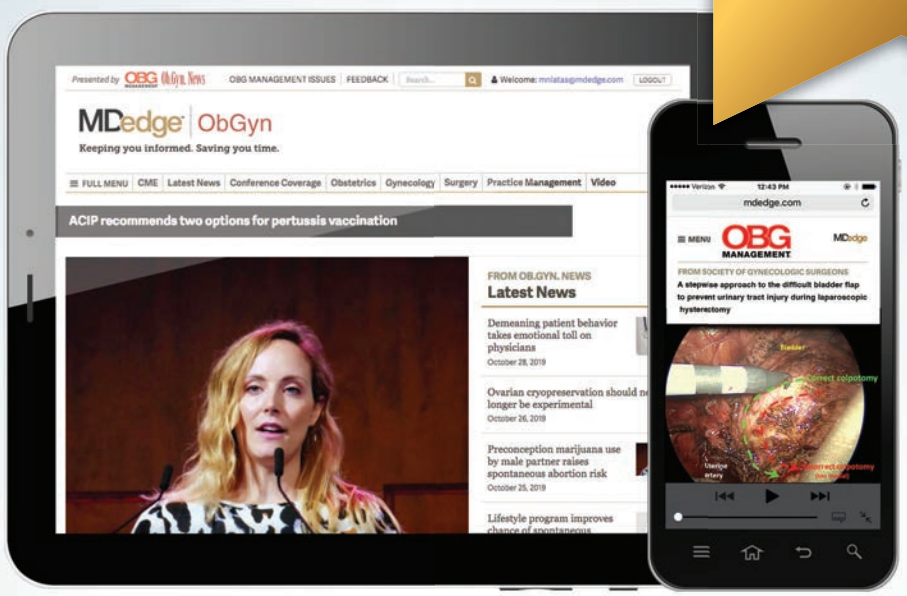

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OBG MANAGEMENT

EDITORIAL

Subclinical hypothyroidism and pregnancy: Public health problem or lab finding with minimal clinical significance?

There is no clear evidence that thyroxine can improve pregnancy outcomes in women with subclinical hypothyroidism

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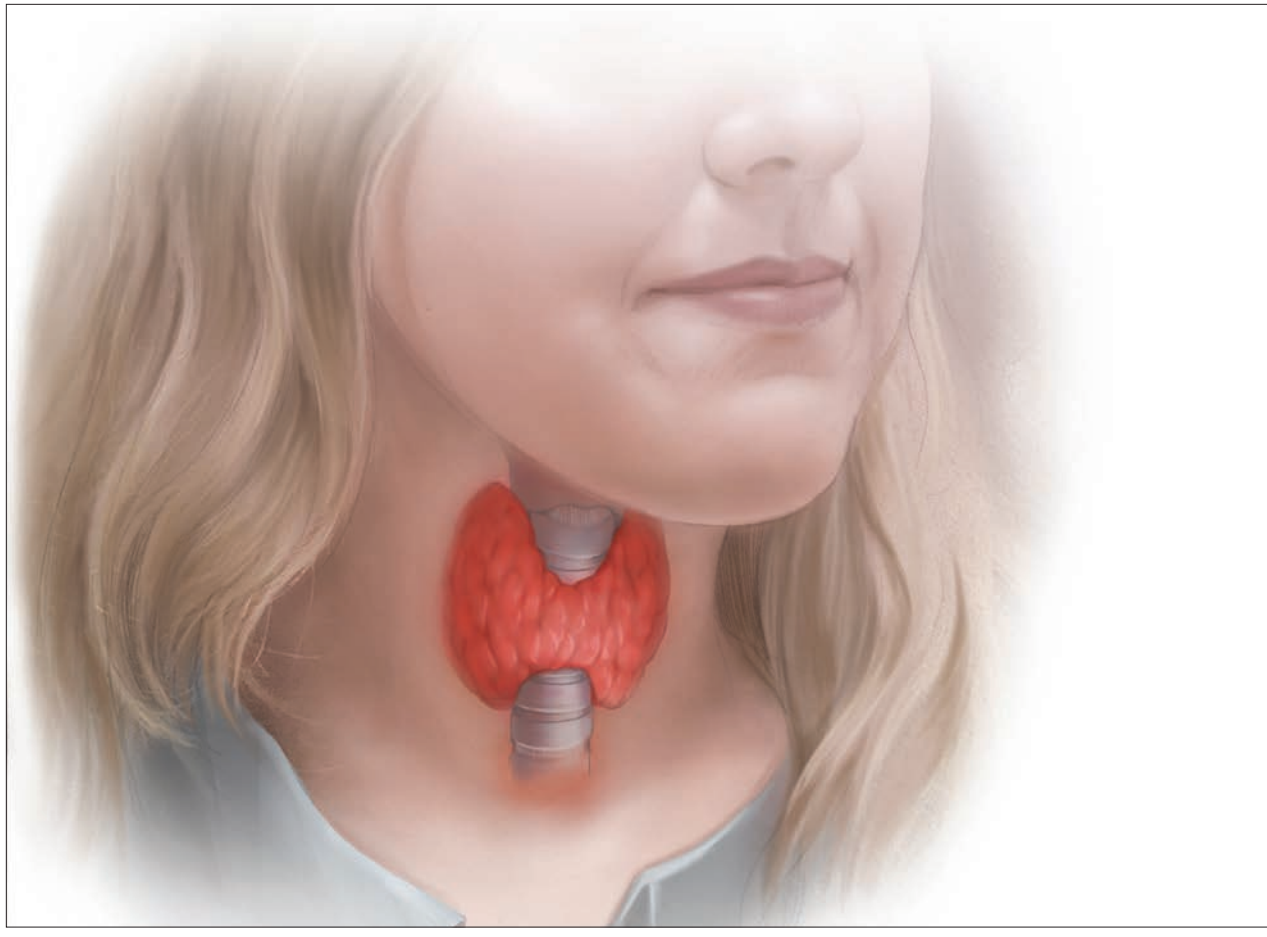
In a US study of more than 17,000 people, overt hypothyroidism and hyperthyroidism were detected in about 4.6% and 1.3% of adults, respectively.[1] In this population-based study, thyroid disease was 5 times more prevalent among women than among men. In our ObGyn practices, there are many women of reproductive age with thyroid disease who are considering pregnancy. Treatment of active hyperthyroidism in a woman planning pregnancy is complex and best managed by endocrinologists. Treatment of hypothyroidism is more straightforward, however, and typically managed by internists, family medicine clinicians, and obstetrician-gynecologists.

Clinical management of hypothyroidism and pregnancy

Pregnancy results in a doubling of thyroxine-binding globulin (TBG) levels and a 40% increase in plasma volume, resulting in a need for more thyroxine production.[2] Of note, from conception to approximately 13 weeks' gestation, the sole source of embryonic and fetal thyroid hormones is from the mother.[2] Women who have been taking chronic thyroxine treatment may have suppressed thyroid gland activity and be unable to increase thyroxine production in response to pregnancy, necessitating a 30% to 50% increase in their thyroxine dose to maintain TSH levels in the normal range.

For hypothyroid women on long-term thyroxine treatment, recommend increasing the thyroxine dose when pregnancy is recognized. For your patients on chronic thyroxine treatment who are planning a pregnancy, a multiprong approach is helpful in preparing the patient for the increased thyroxine requirements of early pregnancy. First, it is important to counsel the woman that she should not stop the thyroxine medication because it may adversely affect the pregnancy. In my experience, most cases of overt hypothyroidism during pregnancy occur because the patient stopped taking her thyroxine therapy. Second, for hypothyroid women who are considering conception it is reasonable to adjust the thyroxine dose to keep the TSH concentration in the lower range of normal (0.5 to 2.5 mU/L). This will give the woman a "buffer," reducing the risk that in early pregnancy she and her fetus will have a thyroxine deficit. Third, in early pregnancy, following detection of a positive pregnancy test, your patient can start to increase her thyroxine dose by about two tablets weekly (a 28% increase in the dose). Fourth, TSH levels can be measured every 4 weeks during the first trimester, with appropriate adjustment of the thyroxine dose to keep the TSH concentration below the trimester-specific upper limit of normal (< 4 mU/L).[2]

TSH and free thyroxine measurements identify women with overt hypothyroidism who need thyroxine treatment. Overt hypothyroidism is associated with adverse reproductive outcomes, including decreased fertility, increased spontaneous abortion, increased fetal loss, and preterm birth.[2,3] Hence it is important to immediately initiate thyroxine treatment in pregnant



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women who have overt hypothyroidism. A diagnosis of overt hypothyroidism is indicated in women with an intact hypothalamic-pituitary axis and a TSH level ≥10 mU/L plus a low free thyroxine concentration. A TSH level of >4 to 10 mU/L, with normal free thyroxine concentration, is evidence of subclinical hypothyroidism (SCH). Among women, there are about 5 times more cases of SCH than overt hypothyroidism.

The literature concerning SCH and pregnancy is vast, and often contradictory, leading to confusion among clinicians. Contributing to the confusion is that some observational studies report a modest association between SCH and adverse pregnancy outcomes. To date, however, randomized clinical trials show no benefit of thyroxine treatment in these cases. I explore these contradictory pieces of evidence below.

Is SCH associated with adverse pregnancy outcomes due to low thyroxine levels?

There is conflicting literature about the association of SCH and adverse reproductive outcomes. A meta-analysis of 47,045 pregnant women reported that the preterm birth rate for women with SCH and euthyroid women (normal TSH and normal free thyroxine levels) was 6.1% and 5.0%, respectively (odds ratio [OR], 1.29; 95% CI, 1.01–1.64).[4] Interestingly, pregnant women with normal TSH levels but a low free thyroxine level also had an increased rate of preterm birth (7.1% vs 5.0%; OR, 1.46; 95% CI, 1.12–1.90).

Although observational studies report an association between SCH and adverse reproductive outcomes, multiple randomized clinical trials conducted in women with SCH or hypothyroxinemia have failed to demonstrate that thyroxine replacement improves reproductive outcomes. For example, in a study of 794 pregnant women with elevated TSH and/or low free thyroxine levels randomly assigned to thyroxine treatment (0.15 mg daily) or no treatment, there was no difference in preterm birth rate (5.6% vs 7.9%, $P = .2$), mean birth weight (3.5 kg vs 3.3 kg, $P = .15$), gestational age at delivery (40.1 vs 40.2 weeks, $P = .10$), or the

intelligence quotient of children at 3 years (99 vs 100, $P = .40$).[5]

In another study, 674 pregnant women with mild SCH (mean TSH, 4.4 mU/L) were randomly assigned to receive thyroxine (0.1 mg daily and dose adjusted to achieve a normal TSH level) or placebo. In this study there was no difference between the thyroxine treatment or placebo groups in preterm birth rate (9% vs 11%, $P = .44$), gestational age at delivery (39.1 vs 38.9 weeks, $P = .57$) or intelligence quotient of children at 5 years (97 and 94, $P = .71$).[6]

The same investigators also randomized 524 pregnant women with isolated hypothyroxinema (mean free thyroxine level, 0.83 ng/dL) and normal TSH level (mean, 1.5 mU/L) to thyroxine (0.05 mg daily and dose adjusted to achieve a normal free thyroxine level) or placebo.[6] In this study there was no difference in preterm birth rate (12% vs 8%, $P = .11$), gestational age at delivery (39.0 vs 38.8 weeks, $P = .46$) or intelligence quotient of children at 5 years (94 and 91, $P = .31$).[6]

When large randomized clinical trials and observational studies report discrepant results, many authorities prioritize the findings from the randomized clinical trials because those results are less prone to being confounded by unrecognized factors. Randomized trials do not demonstrate that mild SCH or isolated hypothyroxinemia have a major impact on pregnancy outcomes.

Thyroid antibodies, fertility, miscarriage, and preterm birth

Some observational studies report that the presence of thyroid antibodies in a euthyroid woman reduces fecundity and increases the risk for miscarriage and preterm birth. For example, a meta-analysis of 47,045 pregnant women reported that the preterm birth rate for women with and without antithyroid antibodies was 6.9% and 4.9%, respectively (OR, 1.33; 95% CI, 1.15–1.56). However, in euthyroid women with antithyroid antibodies, low-dose thyroxine therapy has not been shown to improve fertility, or reduce miscarriages or preterm birth rate.

In a large randomized clinical trial, 952 euthyroid women (normal TSH level; range, 0.44 to 3.63 mIU/L and free thyroxine level; range, 10 to 21 pmol/L) who were planning on conceiving and had elevated thyroid peroxidase antibodies were randomized prior to conception to receive either thyroxine (50 µg) or placebo.[7] After 12 months, outcomes were similar for women treated with thyroxine or placebo, including live birth rate (37.4% vs 37.9%), miscarriage rate for those who became pregnant (28.2% vs 29.6%), and preterm birth ≤ 34 weeks of gestation (3.8% vs 3.6%, respectively).[7] The investigators concluded that the use of low-dose thyroxine in euthyroid women with thyroid peroxidase antibodies was not effective for increasing the rate of live birth or reducing the rate of miscarriage or early preterm birth.

Thyroid antibodies and the rate of IVF pregnancy and miscarriage

Some observational studies suggest that the presence of antithyroid antibodies may be associated with an increased rate of miscarriage.[8] To test the effects of thyroxine treatment on the rate of miscarriage in euthyroid women with antithyroid antibodies, 600 euthyroid infertile women with antithyroid antibodies (antithyroid peroxidase levels ≥ 60 IU/mL) scheduled to have in vitro fertilization (IVF) were randomly assigned to receive thyroxine (dose adjustment to keep TSH levels in the range of 0.1 to 2.5 mIU/L) or no treatment.[9] The thyroxine treatment was initiated 2 to 4 weeks before initiation of ovarian stimulation. In this study, treatment with thyroxine or no treatment resulted in similar rates of clinical pregnancy (35.7% vs 37.7%) and live birth (31.7% vs 32.3%).[9] Among the women who achieved a clinical pregnancy, miscarriage rates were similar in the thyroxine and no treatment groups (10.3% vs 10.6%).[9]

Let's focus on more serious problems that affect pregnancy

There is a clear consensus that women with overt hypothyroidism should be treated with thyroxine prior to attempting pregnancy.[2,6] There is no clear consensus about how to treat women considering pregnancy who have one isolated laboratory finding, such as mild subclinical hypothyroidism, mild isolated hypothyroxinemia, or antithyroid antibodies. Given the lack of evidence from randomized trials that thyroxine improves pregnancy outcomes in these cases, obstetrician-gynecologists may want to either refer women with these problems to an endocrinologist for consultation or sequentially measure laboratory values to assess whether the patient's laboratory abnormality is transient, stable, or worsening.

Obstetrician-gynecologists and their patients are confronted by many serious problems that adversely affect pregnancy and deserve priority attention, including iron deficiency anemia, excess gestational weight gain, peripartum depression, intimate partner

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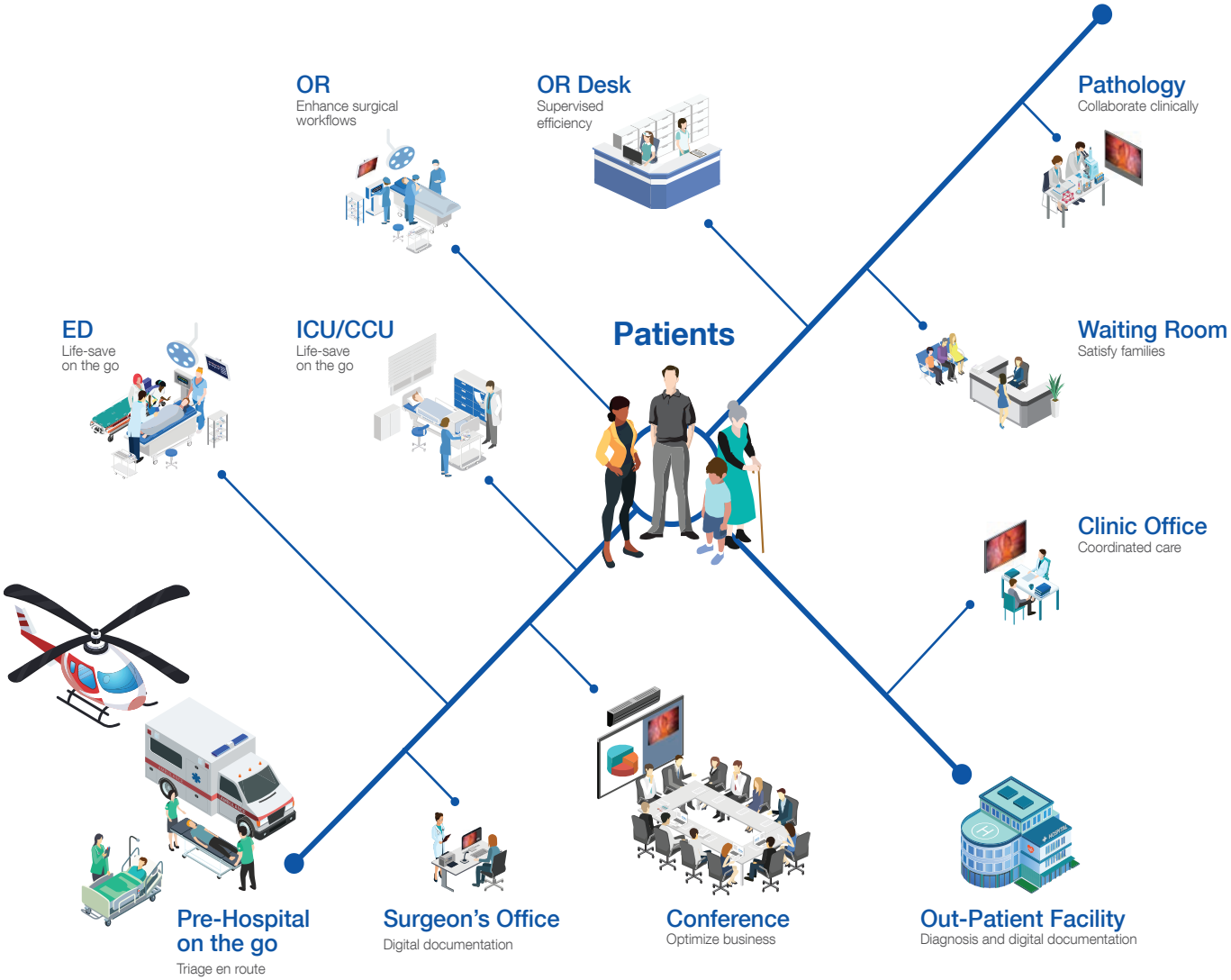

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violence, housing insecurity, cigarette smoking, substance misuse, chronic hypertension, morbid obesity, diabetes, gestational diabetes, preeclampsia, venous thromboembolism, obstetrical hemorrhage, sepsis, and infectious diseases. Given limited resources our expertise should be focused on these major obstetric public health problems rather than screening for mild subclinical hypothyroidism. ●

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Dr. Barbieri reports no financial relationships relevant to this article.

Correction

Per the article authors, in the following article, The case for outpatient cervical ripening for IOL at term for low-risk pregnancies. *OBG Manag.* 2019;31(9):41-48, 52., box 5 of Figure 3 should have read, "50 µg of oral misoprostol administered if nonstress test appropriate." The article has been corrected online.

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Dr. Advincula reports serving as a consultant to AbbVie, ConMed, CooperSurgical, Eximis Surgical, Intuitive Surgical, and Titan Medical and receiving royalties from CooperSurgical. Dr. Guan reports that he is a speaker for Applied Medical. The other authors report no financial relationships relevant to this article.

Requiring a very particular set of surgical skills, the cutting edge vNOTES technique for hysterectomy incorporates conventional laparoscopic instrumentation in a vaginal approach. Here, its pioneers describe how it's done.

IN THIS ARTICLE

Through the years, the surgical approach to hysterectomy has expanded from its early beginnings of being performed only through an abdominal or transvaginal route with traditional surgical clamps and suture. The late 1980s saw the advent of the laparoscopic-assisted vaginal hysterectomy (LAVH), and from that point forward several additional hysterectomy methods evolved, including today's robotic approaches.

Although clinical evidence and societal endorsements support vaginal hysterectomy as a superior high-value modality, it remains one of the least performed among all available routes.[1-3] In an analysis of inpatient hysterectomies published by Wright and colleagues in 2013, 16.7% of hysterectomies were performed vaginally, a number that essentially has remained steady throughout the ensuing years.[4]

Attempts to improve the application of vaginal hysterectomy have been made.[5] These include the development of various curriculum and simulation-based medical education programs on vaginal surgical skills training and acquisition in the hopes of improving utilization.[6] An interesting recent development is the rethinking of vaginal hysterectomy by several surgeons globally who are applying facets of the various hysterectomy methods to a transvaginal approach known as vaginal natural orifice transluminal endoscopic surgery (vNOTES).[7,8] Unique to this thinking is the incorporation of conventional laparoscopic instrumentation.

Although I have not yet incorporated this approach in my surgical armamentarium at Columbia University Medical Center/New York–Presbyterian Hospital, I am intrigued by the possibility that this technique may serve as a rescue for vaginal hysterectomies that are at risk of conversion or of not being performed at all.[9]

At this time, vNOTES is not a standard of care and should be performed only by highly

specialized surgeons. However, in the spirit of this Update on minimally invasive surgery and to keep our readers abreast of burgeoning techniques, I am delighted to bring you this overview by Dr. Xiaoming Guan, one of the pioneers of this surgical approach, and Dr. Tamisa Koythong and Dr. Juan Liu. I hope you find this recent development in hysterectomy of interest.

—ARNOLD P. ADVINCULA, MD

Development and evolution of NOTES

Over the past few decades, emphasis has shifted from laparotomy to minimally invasive surgery because of its proven significant advantages in patient care, such as improved cosmesis, shorter hospital stay, shorter postoperative recovery, and decreased postoperative pain and blood loss.[10] Advances in laparoendoscopic surgery and instrumentation, including robot-assisted laparoscopy (RAL), single-incision laparoscopic surgery (SILS), and most recently natural orifice transluminal endoscopic surgery (NOTES), reflect ongoing innovative developments in the field of minimally invasive surgery.

Here, we provide a brief literature review of the NOTES technique, focus on its application in gynecologic surgery, and describe how we perform NOTES at our institution.

FAST TRACK

With NOTES, peritoneal access is gained through a natural orifice—the mouth, vagina, urethra, or anus—to perform endoscopic surgery

NOTES application in gynecology

With NOTES, peritoneal access is gained through a natural orifice (such as the mouth, vagina, urethra, or anus) to perform endoscopic surgery, occasionally without requiring an abdominal incision. First described in 2004, transgastric peritoneoscopy was performed in a porcine model, and shortly thereafter the first transgastric appendectomy was performed in humans.[11,12] The technique has further been adopted in cholecystectomy, appendectomy, gastrectomy, and nephrectomy procedures.[13]

Given rapid interest in a possible paradigm shift in the field of minimally invasive surgery, the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) was formed, and the group published an article on potential barriers to accepted practice and adoption of NOTES as a realistic alternative to traditional laparoscopic surgery.[14]

While transgastric and transanal access to the peritoneum were initially more popular, the risk of anastomotic leaks associated with incomplete closure and subsequent infection were thought to be prohibitively high.[15] Transvaginal access was considered a safer and simpler alternative, allowing for complete closure without increased risk of infection, and this is now the route through which the majority of NOTES procedures are completed.[16,17]

The eventual application of NOTES in the field of gynecology seemed inevitable. The American College of Obstetricians and Gynecologists stated that transvaginal surgery is the most minimally invasive and preferred surgical route in the management of patients with benign gynecologic diseases.[18] However, performing it can be challenging at times due to limited visualization and lack of the required skills for single-site surgery. NOTES allows a gynecologic surgeon to improve visualization through the use of laparoendoscopic instruments and to complete surgery through a transvaginal route.

In 2012, Ahn and colleagues demonstrated the feasibility of the NOTES technique in gynecologic surgery after using it to successfully complete benign adnexal surgery in 10 patients.[19] Vaginal NOTES (vNOTES) has since been further developed to include successful hysterectomy, myomectomy, sacrocolpopexy, tubal anastomosis, and even

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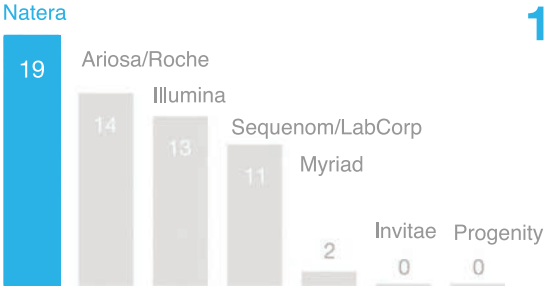

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Clearly, vNOTES is the next exciting development in minimally invasive surgery, improving patient outcomes and satisfaction with truly scarless surgery. Compared with traditional transvaginal surgery, vNOTES has the advantage of improved visualization with laparoendoscopic guidance, and it may be beneficial even for patients previously thought to have relative contraindications to successful completion of transvaginal surgery, such as nulliparity or a narrow introitus.

lymphadenectomy in the treatment of early-stage endometrial carcinoma.[20-26] vNOTES also can be considered a rescue approach for traditional vaginal hysterectomy in instances in which it is necessary to evaluate adnexal pathology.[9] Most recently, vNOTES hysterectomy has been reported with da Vinci Si or Xi robotic platforms.[27,28]

Operative time, post-op stay shorter in NAOC-treated patients

Few studies have compared outcomes with vNOTES to those with traditional laparoscopy. In 2016, Wang and colleagues compared surgical outcomes between NOTES-assisted ovarian cystectomy (NAOC) and laparoscopic ovarian cystectomy (LOC) in a case-matched study that included 277 patients.[29] Although mean (SD) blood loss in patients who underwent LOC was significantly less compared with those who underwent NAOC (21.4 [14.7] mL vs 31.6 [24.1] mL; P = .028), absolute blood loss in both groups was deemed minimal. Additionally, mean (SD) operative time and postoperative stay were significantly less in patients undergoing NAOC compared with those having LOC (38.23 [10.19] minutes vs 53.82 [18.61] minutes; $P \leq .001$; and 1.38 [0.55] days vs 1.82 [0.52] days; $P \leq .001$; respectively).[29]

FAST TRACK

In a study of vNOTES versus TLH, vNOTES hysterectomy was associated with shorter operative time, shorter hospital stay, and lower postoperative analgesic requirement

How vNOTES hysterectomy stacked up against TLH

In 2018, Baekelandt and colleagues compared outcomes between vNOTES hysterectomy and total laparoscopic hysterectomy (TLH) in a noninferiority single-blinded trial of 70 women.[8] Compared with TLH, vNOTES hysterectomy was associated with shorter operative time (41 vs 75 minutes; P<.001), shorter hospital stay (0.8 vs 1.3 days; P = .004), and lower postoperative analgesic requirement (8 vs 14 U; P = .006). Additionally, there were no differences between the 2 groups in postoperative infection rate, intraoperative complications, or hospital readmissions within 6 weeks.[8]

Approach for performing vNOTES procedures

At our institution, Baylor College of Medicine, the majority of gynecologic surgeries are performed via either transumbilical robot-assisted single-incision laparoscopy or vNOTES. Preoperative selection of appropriate candidates for vNOTES includes:

- low suspicion for or prior diagnosis of endometriosis with obliteration of the posterior cul-de-sac
- no surgical history suggestive of severe adhesive disease, and
- adequate vaginal sidewall access and sufficient descent for instrumentation for entry into the peritoneal cavity.

In general, a key concept in vNOTES is "vaginal pull, laparoscopic push," which means that the surgeon must pull the cervix while performing vaginal entry and then push the uterus back in the peritoneal cavity to

increase surgical space during laparoscopic surgery.

Overview of vNOTES steps

Below we break down a description of vNOTES in 6 sections. Our patients are always placed in dorsal lithotomy position with TrenGuard (D.A. Surgical) Trendelenburg restraint. We prep the abdomen in case we need to convert to transabdominal surgery via transumbilical single-incision laparoscopic surgery or traditional laparoscopic surgery.

1. Vaginal entry

Accessing the peritoneal cavity through the vagina initially proceeds like a vaginal hysterectomy. We inject dilute vasopressin (20 U in 20 mL of normal saline) circumferentially in the cervix (for hysterectomy) or in the posterior cervix in the cervicovaginal junction (for adnexal surgery without hysterectomy) for vasoconstriction and hydrodissection.

We then incise the vaginal mucosa circumferentially with electrosurgical cautery and follow with posterior colpotomy. We find that reapproximating the posterior peritoneum to the posterior vagina with either figure-of-8 stitches or a running stitch of polyglactin 910 suture (2-0 Vicryl) assists in port placement, bleeding at the peritoneal edge, and closure of the cuff or colpotomy at the end of the case. We tag this suture with a curved hemostat.

Depending on whether a hysterectomy is being performed, anterior colpotomy is made. Again, the anterior peritoneum is then tagged to the anterior vaginal cuff in similar fashion, and this suture is tagged with a different instrument; we typically use a straight hemostat or Sarot clamp (**FIGURE 1**).

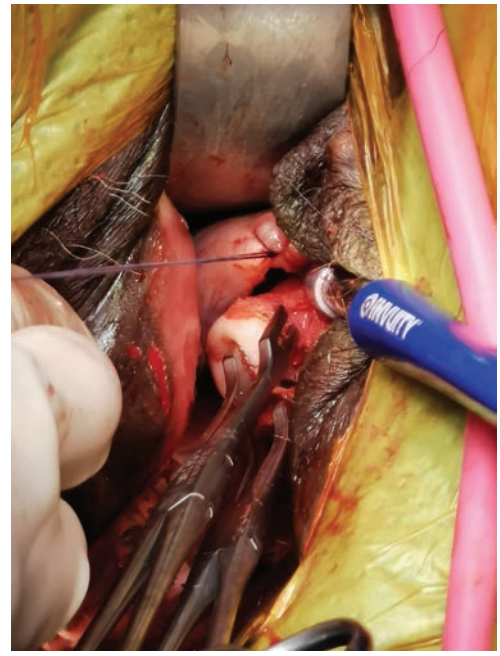

FIGURE 1 Reapproximation of the anterior peritoneum to the anterior vaginal cuff

FAST TRACK

Reapproximating the posterior peritoneum to the posterior vagina with either figure-of-8 stitches or a running stitch of polyglactin suture assists in port placement, bleeding at the peritoneal edge, and closure of the cuff or colpotomy at the end of the case

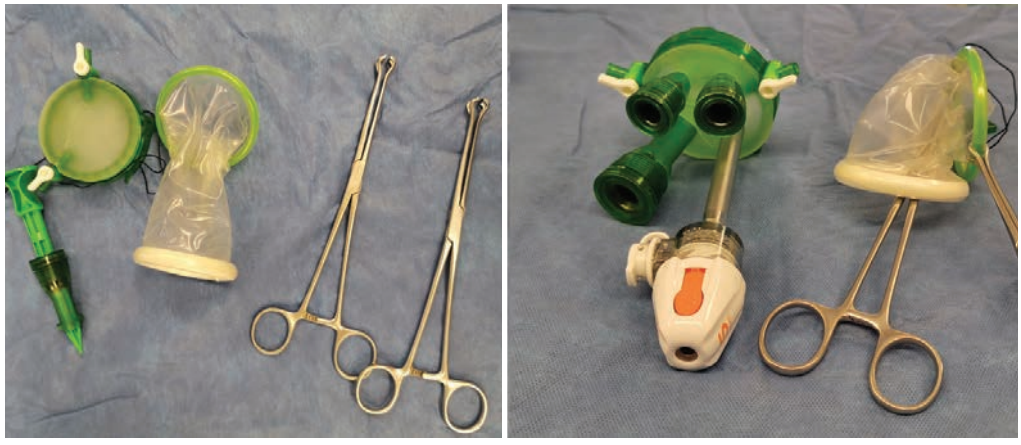

FIGURE 2 The GelPOINT Mini advanced access platform (Applied Medical) displayed with included trocars and Alexis wound protector before (left) and after assembly (right)

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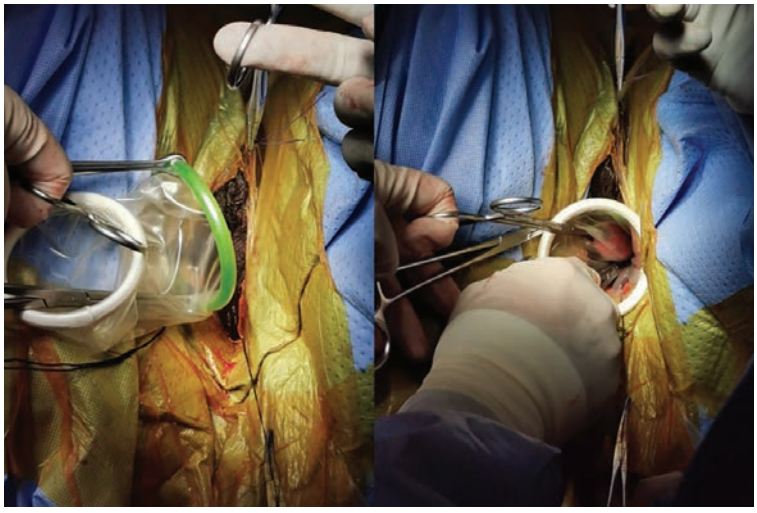

FIGURE 3 Delivering the cervix through the Alexis wound protector. Once delivered, the cervix is regrasped. The assistant surgeon holds the previously tagged sutures parallel to the longitudinal axis of the vagina while the surgeon places the green rigid ring of the Alexis wound protector in the peritoneal cavity.

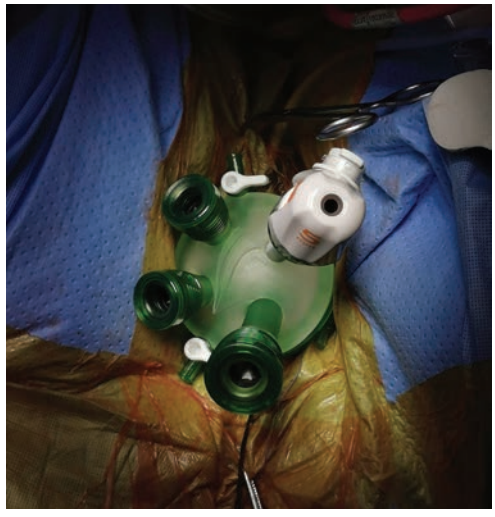

FIGURE 4 Securement of the GelSeal cap on the Alexis wound protector. Location of ports, including a 5-mm AirSeal system port (CONMED), is shown.

2. Traditional vaginal hysterectomy

After colpotomy, we prefer to perform progressive clamping of the broad ligament from the uterosacral and cardinal ligaments to the level of uterine artery as in traditional vaginal hysterectomy, if feasible.

3. Single-site port placement

The assembled GelPOINT Mini advanced access platform (Applied Medical) (**FIGURE 2**, page 21) is introduced through the vagina after the Alexis wound protector (included with the kit) is first placed through the colpotomy with assistance of Babcock clamps (**FIGURE 3**).

After ensuring that the green rigid ring of the Alexis wound protector is contained and completely expanded within the peritoneal cavity, we cross our previously tagged sutures as we find this helps with preventing the GelPOINT Mini access platform from inadvertently shifting out of the peritoneal cavity during surgery. The GelSeal cap is then secured and pneumoperitoneum is established (**FIGURE 4**).

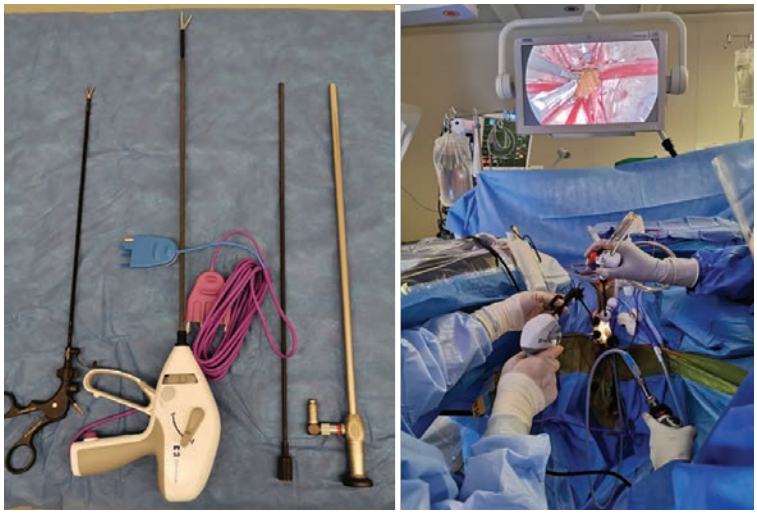

FIGURE 5 Laparoscopic instruments used in vNOTES prior to complete assembly (left) and their use during surgery with 2 surgeons (right). The laparoscopic instruments are of different lengths, which is paramount to successful vNOTES.

4. Laparoendoscopic surgery

Instruments used in our surgeries include a 10-mm rigid 30° 43-cm working length laparoscope; a 44-cm LigaSure device (Medtronic); a 5-mm, 37-cm laparoscopic cobra grasping forceps and fenestrated grasper (Karl Storz); and a 5-mm, 45-cm laparoscopic suction with hydrodissection tip (Stryker) (**FIGURE 5**).

vNOTES allows a gynecologic surgeon the unique ability to survey the upper abdomen. The remainder of the surgery proceeds using basic laparoscopic single-site skills.

During vNOTES, as with all single-site

CONTINUED ON PAGE 28

Symptoms of **postpartum depression** (PPD) can have a negative impact on mothers. If left untreated, these symptoms may persist for months or up to a year.[1]

Not an actual patient.

INDICATION

ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.

Select IMPORTANT SAFETY INFORMATION for ZULRESSO

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration.

Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).

Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

Zulresso™
(brexanolone) injection IV
for intravenous use 100mg/20mL

Please see Full Important Safety Information and Brief Summary of Full Prescribing Information, including Boxed Warning, on adjacent pages.

Individual results may vary.

Not an actual patient.

STUDY DESIGN[2,3]

The efficacy of ZULRESSO in the treatment of PPD was demonstrated in two multicenter, randomized, double-blind, placebo-controlled studies (referred to as Studies 1 and 2) in women (18 to 45 years) with PPD who met the *Diagnostic and Statistical Manual of Mental Disorders* criteria for a major depressive episode (*DSM-IV*) with onset of symptoms in the third trimester or within 4 weeks of delivery. Women were enrolled up to 6 months postpartum. In these studies, patients received a 60-hour continuous intravenous infusion of ZULRESSO or placebo and were then followed for 4 weeks. Study 1 (NCT02942004) included patients with severe PPD (HAM-D score ≥26), and Study 2 (NCT02942017) included patients with moderate PPD (HAM-D score of 20 to 25). A titration to the recommended target dosage of 90 mcg/kg/hour was evaluated in both studies (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 20 hours, 90 mcg/kg/hour for 28 hours, followed by a taper to 60 mcg/kg/hour for 4 hours and then 30 mcg/kg/hour for 4 hours). A titration to a target dosage of 60 mcg/kg/hour (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 52 hours, then 30 mcg/kg/hour for 4 hours) was also evaluated in Study 1.

The safety of ZULRESSO was evaluated across 3 clinical trials (a Phase II study, Study 1, and Study 2) in 140 women who were exposed to ZULRESSO. The Phase II study evaluated 21 women with severe PPD, 10 of whom received a dose of 90 mcg/kg/hour of ZULRESSO. Baseline oral antidepressant use was reported for 23% of patients.

The primary endpoint was the mean change from baseline in depressive symptoms as measured by the HAM-D total score at the end of the infusion (Hour 60). A pre-specified secondary efficacy endpoint was the mean change from baseline in HAM-D total score at Day 30.

Select IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Excessive Sedation and Sudden Loss of Consciousness: In clinical studies, 5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients experienced sedation and somnolence that required dose interruption or reduction. Loss of consciousness or altered state of consciousness was reported in 4% of ZULRESSO-treated patients compared with 0% of placebo-treated patients.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of ZULRESSO have dissipated.

ZULRESSO, the **FIRST AND ONLY** FDA-approved treatment indicated for postpartum depression.

Zulresso™
(brexanolone) injection IV
for intravenous use 100mg/20mL

Each. Day. Matters.

RAPID AND SIGNIFICANT IMPROVEMENT OF DEPRESSIVE SYMPTOMS IN 2.5* DAYS[2]

Study 1

62.3% reduction in mean HAM-D total score at Hour 60 with ZULRESSO 90 mcg/kg/hour (n=41)† vs 49.0% with placebo (n=43†; *P*=0.0252‡)

In a group of 38 patients in Study 1, a ZULRESSO titration to a target dose of 60 mcg/kg/hour was also superior to placebo in improvement of depressive symptoms.

The recommended dosage of ZULRESSO is 90 mcg/kg/hour.
HAM-D=Hamilton Depression Rating Scale.

Study 2

64.6% reduction in mean HAM-D total score at Hour 60 with ZULRESSO 90 mcg/kg/hour (n=51)† vs 53.3% with placebo (n=53†; *P*=0.0160‡)

*2.5 days=Hour 60.
†Intention to treat population.
‡Statistically significant after multiplicity adjustments.

Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program called the ZULRESSO REMS.

Warnings and precautions for ZULRESSO include: risk of excessive sedation, risk of sudden loss of consciousness, and suicidal thoughts and behaviors.

Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

Use in specific populations:

- Pregnancy: May cause fetal harm
- Avoid use in patients with end stage renal disease (ESRD)

Select IMPORTANT SAFETY INFORMATION

ZULRESSO Risk Evaluation and Mitigation Strategy (REMS):
Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379

For more information about ZULRESSO treatment and access, visit ZulressoHCP.com

Please see Full Important Safety Information and Brief Summary of Full Prescribing Information, including Boxed Warning, on the following pages.

References: 1. Vliegen N, Casalin S, Luyten P. The course of postpartum depression: a review of longitudinal studies. *Harv Rev Psychiatry*. 2014;22(1):1-22. **2.** ZULRESSO Prescribing Information. Cambridge, MA: Sage Therapeutics, Inc; 6/2019. **3.** Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet*. 2018;392(10152):1058-1070.

INDICATION

ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.

IMPORTANT SAFETY INFORMATION for ZULRESSO

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration.

Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).

Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

WARNINGS AND PRECAUTIONS

Excessive Sedation and Sudden Loss of Consciousness:
In clinical studies, 5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients experienced sedation and somnolence that required dose interruption or reduction. Loss of consciousness or altered state of consciousness was reported in 4% of ZULRESSO-treated patients compared with 0% of placebo-treated patients.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of ZULRESSO have dissipated.

ZULRESSO Risk Evaluation and Mitigation Strategy (REMS): ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm.

Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379.

SUICIDAL THOUGHTS AND BEHAVIORS

In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that include approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD).

ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. If depression becomes worse or patients experience emergent suicidal thoughts and behaviors, consider changing the therapeutic regimen, including discontinuing ZULRESSO.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm

  There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including ZULRESSO, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/
- **Lactation:** Brexanolone is transferred to breastmilk in nursing mothers. There are no data on the effects of ZULRESSO on a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition
- **Pediatric Use:** The safety and effectiveness of ZULRESSO in pediatric patients have not been established
- **Renal Impairment:** No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment. Avoid use of ZULRESSO in patients with end stage renal disease (ESRD)

CONTROLLED SUBSTANCE

ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-4-SAGERX (1-844-472-4379) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Zulresso™ (brexanolone) injection IV
for intravenous use 100mg/20mL

For more information about ZULRESSO treatment and access, visit ZulressoHCP.com

Sage Therapeutics™

Please see Brief Summary of Full Prescribing Information, including Boxed Warning, on the following pages.

ZULRESSO™ (brexanolone) injection Ⓘⓥ, for intravenous use

Rx only

BRIEF SUMMARY OF PRESCRIBING INFORMATION

(For complete details, please see *Full Prescribing Information, including Boxed Warning, and Medication Guide.*)

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

- **Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO.**
- **Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).**
- **Because of these risks, ZULRESSO is available only through a restricted program called the ZULRESSO REMS.**

1 INDICATIONS AND USAGE: ZULRESSO™ is indicated for the treatment of postpartum depression (PPD) in adults.

2 DOSAGE AND ADMINISTRATION

A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion.

Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows:

- 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
- 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
- 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)
- 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
- 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour

Dilution required prior to administration.

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Excessive Sedation and Sudden Loss of Consciousness In clinical studies, ZULRESSO caused sedation and somnolence that required dose interruption or reduction in some patients during the infusion (5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients). Some patients were also reported to have loss of consciousness or altered state of consciousness during the ZULRESSO infusion (4% of the ZULRESSO-treated patients compared with 0% of the placebo-treated patients). Time to full recovery from loss or altered state of consciousness, after dose interruption, ranged from 15 to 60 minutes. A healthy 55-year-old man participating in a cardiac repolarization study experienced severe somnolence and <1 minute of apnea while receiving two times the maximum recommended dosage of ZULRESSO (180 mcg/kg/hour). All patients with loss of or altered state of consciousness recovered with dose interruption.

There was no clear association between loss or alteration of consciousness and pattern or timing of dose. Not all patients who experienced a loss or alteration of consciousness reported sedation or somnolence before the episode.During the infusion, monitor patients for sedative effects every 2 hours during planned, non sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation.

After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate.

Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia,the infusion should not be resumed.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving after infusion until any sedative effects of ZULRESSO have dissipated. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness. Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation.

Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

5.2 ZULRESSO Risk Evaluation and Mitigation Strategy (REMS) ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm. Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO.
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379.

5.3 Suicidal Thoughts and Behavior In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range (years)	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18-24	5 additional patients
	Decreases Compared to Placebo
25-64	1 fewer patient

*ZULRESSO is not approved in pediatric patients.

ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. Consider changing the therapeutic regimen, including discontinuing ZULRESSO, in patients whose depression becomes worse or who experience emergent suicidal thoughts and behaviors.

6 ADVERSE REACTIONS The following adverse reactions are discussed in more detail in other sections of the labeling:

- Excessive Sedation and Sudden Loss of Consciousness

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to ZULRESSO in 140 patients with postpartum depression (PPD). A titration to a target dosage of 90 mcg/kg/hour was evaluated in 102 patients and a titration to a target dose of 60 mcg/kg/hour was evaluated in 38 patients. Patients were then followed for 4 weeks.

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush (Table 2).

Adverse Reactions Leading to Discontinuation, Dosage Interruption, or Dosage Reduction

In the pooled placebo controlled-studies, the incidence of patients who discontinued due to any adverse reaction was 2% of ZULRESSO-treated patients compared to 1% of placebo treated patients. The adverse reactions leading to treatment discontinuation in ZULRESSO-treated patients were sedation-related (loss of consciousness, vertigo, syncope, and presyncope) or infusion site pain.

In the pooled placebo controlled-studies, the incidence of patients who had an interruption or reduction of the dosage due to any adverse reaction was 7% of ZULRESSO treated patients compared to 3% of placebo-treated patients. The adverse reactions leading to dose reduction or interruption in ZULRESSO-treated patients were sedation-related (loss of consciousness, syncope, somnolence, dizziness, fatigue), infusion site events, changes in blood pressure, or medication error due to infusion pump malfunction. Three ZULRESSO-treated patients who had a dosage interruption because of loss of consciousness subsequently resumed and completed treatment after resolution of symptoms; two patients who had dosage interruption because of loss of consciousness did not resume the infusion.

Table 2 presents the adverse reactions that occurred in ZULRESSO-treated PPD patients at a rate of at least 2% and at a higher rate than in the placebo-treated patients during the 60 hour treatment period.

Table 2: Adverse Reactions in Placebo-Controlled Studies in Patients with PPD Reported in ≥ 2% of ZULRESSO-Treated Patients and Greater than Placebo-Treated Patients

	Placebo (n=107)	Maximum dosage 60 mcg/kg/hour (n=38)	Maximum dosage 90 mcg/kg/hour (Recommended dosage) (n=102)
Cardiac Disorders			
Tachycardia	-	-	3%
Gastrointestinal Disorders			
Diarrhea	1%	3%	2%
Dry mouth	1%	11%	3%
Dyspepsia	-	-	2%
Oropharyngeal pain	-	3%	2%
Nervous System Disorders			
Dizziness, presyncope, vertigo	7%	13%	12%
Loss of consciousness	-	5%	3%
Sedation, somnolence	6%	21%	13%
Vascular Disorders			
Flushing, hot flush	-	5%	2%

7 DRUG INTERACTIONS

7.1 CNS Depressants Concomitant use of ZULRESSO with CNS depressants (e.g., opioids, benzodiazepines) may increase the likelihood or severity of adverse reactions related to sedation.

7.2 Antidepressants In the placebo-controlled studies, a higher percentage of ZULRESSO-treated patients who used concomitant antidepressants reported sedation-related events.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/.

Risk Summary

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm. There are no available data on ZULRESSO use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, malformations were not seen in rats or rabbits at plasma levels up to 5 and 6 times the maximum recommended human dose (MRHD), respectively. Developmental toxicities were seen in the fetuses of rats and rabbits at 5 and ≥3 times the plasma levels at the MRHD, respectively. Reproductive toxicities were seen in rabbits at ≥3 times the plasma levels at the MRHD. These effects were not seen in rats and rabbits at 2 and 1.2 times the plasma levels at the MRHD. Brexanolone administered to pregnant rats during pregnancy and lactation resulted in lower pup survival at doses which were associated with ≥2 times the plasma levels at the MRHD and a neurobehavioral deficit in female offspring at 5 times the plasma levels at the MRHD. These effects were not seen at 0.8 times and 2 times the plasma levels at the MRHD, respectively.

In published animal studies, administration of other drugs that enhance GABAergic inhibition to neonatal rats caused widespread apoptotic neurodegeneration in the developing brain. The window of vulnerability to these changes in rats (postnatal days 0-14) corresponds to the period of brain development that takes place during the third trimester of pregnancy in humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In pregnant rats and rabbits, no malformations were seen when brexanolone was given during the period of organogenesis at continuous intravenous doses up to 60 and 30 mg/kg/day, respectively. These doses were associated with maternal plasma levels 5 and 6 times the plasma levels at the MRHD of 90 mcg/kg/hour, in rats and rabbits, respectively. In rats, a decrease in fetal body weights was seen at 60 mg/kg/day (5 times the plasma level at the MRHD). In rabbits, increased numbers of late resorptions and a decrease in fetal body weights were seen at doses equal to and greater than 15 mg/kg/day (3 times the plasma levels at the MRHD) with fewer live fetuses and a higher post implantation loss seen at 30 mg/kg/day (6 times the plasma levels at the MRHD) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain and/or body weight loss). Effects in rats and rabbits were not seen at 2 and 1.2 times the plasma levels at the MRHD, respectively.

When brexanolone was administered to pregnant rats by continuous intravenous administration at 30 and 60 mg/kg/day (2 and 5 times plasma levels at the MRHD, respectively) during the period of organogenesis and throughout pregnancy and lactation, increased numbers of dead pups and fewer live pups at birth were seen. This effect was not seen at 0.8 times the plasma levels at the MRHD. Decreased pup viability between postnatal day 0 and 4 in the presence of maternal toxicity (decreased body weight gain and food consumption during lactation) was seen at 5 times the plasma levels at the MRHD. These effects were not seen at 2 times the plasma levels at the MRHD. A neurobehavioral deficit, characterized by slower habituation in the maximal startle response in the auditory startle test, was seen in female offspring of dams dosed at 5 times the plasma levels at the MRHD. This effect was not seen at 2 times the plasma levels at the MRHD.

8.2 Lactation

Risk Summary

Available data from a lactation study in 12 women indicate that brexanolone is transferred to breastmilk in nursing mothers. However, the relative infant dose (RID) is low, 1% to 2% of the maternal weight-adjusted dosage. Also, as ZULRESSO has low oral bioavailability (<5%) in adults, infant exposure is expected to be low. There were no reports of effects of ZULRESSO on milk production. There are no data on the effects of ZULRESSO on a breastfed infant. Available data on the use of ZULRESSO during lactation do not suggest a significant risk of adverse reactions to breastfed infants from exposure to ZULRESSO. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.

Data

A study was conducted in twelve healthy adult lactating women treated with intravenous ZULRESSO according to the recommended 60-hour dosing regimen (maximum dosage was 90 mcg/kg/hour). Concentrations of ZULRESSO in breast milk were at low levels (<10 ng/mL) in >95% of women by 36 hours after the end of the infusion of ZULRESSO. The calculated maximum relative infant dose for ZULRESSO during the infusion was 1% to 2%.

8.4 Pediatric Use The safety and effectiveness of ZULRESSO in pediatric patients have not been established.

8.5 Geriatric Use PPD is a condition associated with pregnancy; there is no geriatric experience with ZULRESSO.

8.6 Hepatic Impairment Dosage adjustment in patients with hepatic impairment is not necessary. Modest increases in exposure to unbound brexanolone and modest decreases in exposure to total brexanolone were observed in patients with moderate to severe hepatic impairment (Child-Pugh≥7) with no associated change in tolerability.

8.7 Renal Impairment No dosage adjustment is recommended in patients with mild (eGFR 60 to 89 mL/minute/1.73 m^2), moderate (eGFR 30 to 59 mL/minute/1.73 m^2) or severe (eGFR 15 to 29 mL/minute/1.73 m^2) renal impairment.

Avoid use of ZULRESSO in patients with end stage renal disease (ESRD) with eGFR of < 15 mL/minute/1.73 m^2 because of the potential accumulation of the solubilizing agent, betadex sulfobutyl ether sodium.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

9.2 Abuse In a human abuse potential study, 90 mcg/kg, 180 mcg/kg (two times the maximum recommended infusion rate), and 270 mcg/kg (three times the maximum recommended infusion rate) ZULRESSO infusions over a one hour period were compared to oral alprazolam administration (1.5 mg and 3 mg). On positive subjective measures of "drug liking", "overall drug liking", "high" and "good drug effects", the 90 mcg/kg dosage produced scores that were similar to placebo. Scores on these positive subjective measures for both dosages of ZULRESSO 90 mcg/kg and 180 mcg/kg were lower than both alprazolam doses. However, the scores on the positive subjective measures for ZULRESSO 270 mcg/kg dosage were similar to those produced by both doses of alprazolam. In this study, 3% of subjects administered ZULRESSO 90 mcg/kg and 13% administered ZULRESSO 270 mcg/kg reported euphoric mood, compared to none administered placebo during the one-hour administration.

9.3 Dependence In the PPD clinical studies conducted with ZULRESSO, end of treatment occurred through tapering. Thus, in these studies it was not possible to assess whether abrupt discontinuation of ZULRESSO produced withdrawal symptoms indicative of physical dependence. It is recommended that ZULRESSO be tapered according to the dosage recommendations, unless symptoms warrant immediate discontinuation.

10 OVERDOSAGE

Human Experience

There is limited clinical trial experience regarding human overdosage with ZULRESSO. In premarketing clinical studies, two cases of accidental overdosage due to infusion pump malfunction resulted in transient loss of consciousness. Both patients regained consciousness approximately 15 minutes after discontinuation of the infusion without supportive measures. After full resolution of symptoms, both patients subsequently resumed and completed treatment. Overdosage may result in excessive sedation, including loss of consciousness and the potential for accompanying respiratory changes.

Management of Overdose

In case of overdosage, stop the infusion immediately and initiate supportive measures as necessary. Brexanolone is rapidly cleared from plasma. Consult a Certified Poison Control Center at **1-800-222-1222** for latest recommendations.

PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

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June 2019

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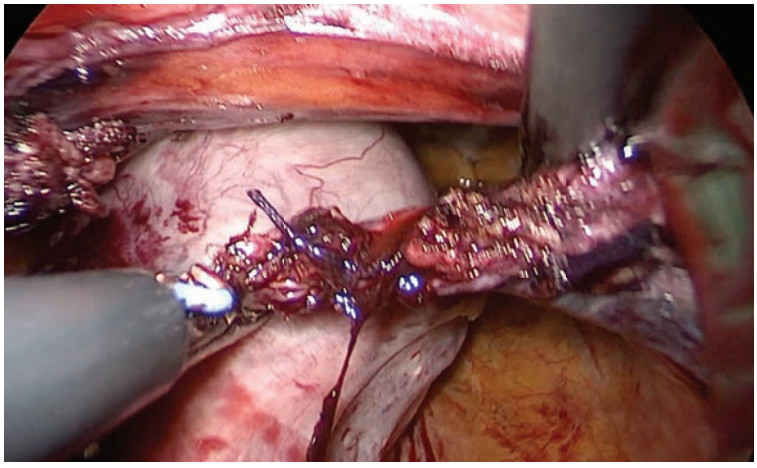

FIGURE 6 Crossed instruments while securing the left uterine artery

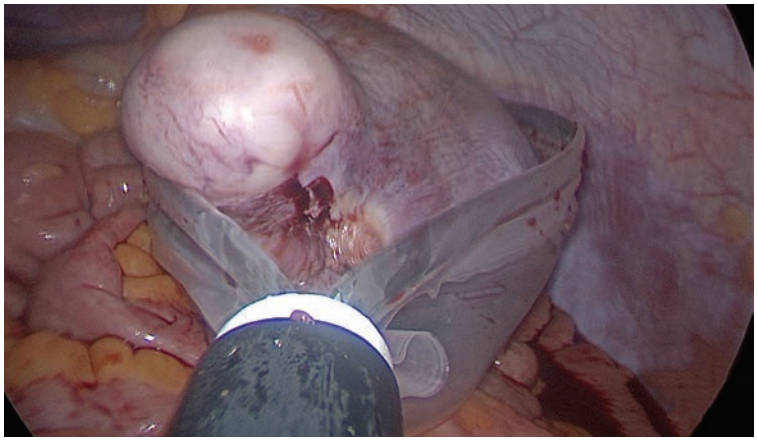

FIGURE 7 Placement of specimen that requires morcellation in a 15-mm Endo Catch specimen retrieval bag

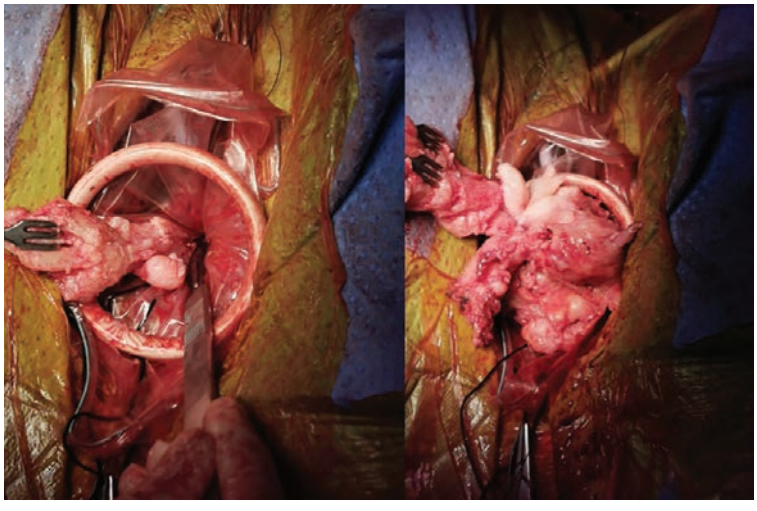

FIGURE 8 Contained bag morcellation with "big C" technique

surgical procedures, understanding the optimal placement of crossed instruments is important for successful completion. For example, when securing the right uterine artery, the surgeon needs to push the cervix toward the patient's left and slightly into the peritoneal cavity using a laparoscopic cobra grasper with his or her left hand while then securing the uterine pedicle using the LigaSure device with his or her right hand. This is then reversed when securing the left uterine artery, where the assistant surgeon pushes the cervix toward the patient's right while the surgeon secures the pedicle ("vaginal pull, laparoscopic push") (**FIGURE 6**).

This again is reiterated in securing the ovarian pedicles, which are pushed into the peritoneal cavity while being secured with the LigaSure device.

5. Specimen removal

For large uteri or specimens that need morcellation, a 15-mm Endo Catch specimen retrieval bag (Medtronic) is introduced through the GelPOINT Mini system. The specimen is then placed in the bag and delivered to the vagina, where contained bag morcellation is performed in standard fashion (**FIGURES 7 AND 8**). We utilized the "big C" technique by first grasping the specimen with a penetrating clamp. The clamp is then held in our nondominant hand and a No. 10 blade scalpel is used to create a reverse c-incision, keeping one surface of the specimen intact. This is continued until the specimen can be completely delivered through the vagina.

Specimens that do not require morcellation can be grasped laparoscopically, brought to the GelPOINT Mini port, which is quickly disassembled, and delivered. The GelSeal cap is then reassembled.

6. Vaginal cuff closure

The colpotomy or vaginal cuff is closed with barbed suture continuously, as in traditional vaginal hysterectomy cuff closure. Uterosacral ligament suspension should be performed for vaginal cuff support. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

vNOTES is the most recent innovative development in the field of minimally invasive surgery, and it has demonstrated feasibility and safety in the fields of general surgery, urology, and gynecology. Adopting vNOTES in clinical practice can improve patient satisfaction and cosmesis as well as surgical outcomes. Gynecologic surgeons can think of vNOTES hysterectomy as "placing an eye" in the vagina while performing transvaginal hysterectomy. The surgical principle of "vaginal pull, laparoscopic push" facilitates the learning process.

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WATCH FOR...

›› Update on bone health

By Steven R. Goldstein, MD, NCMP, CCD

Medical management of abnormal uterine bleeding in reproductive-age women

Appropriate clinical evaluation, laboratory assessment, and management can make the difference for many women with AUB, and avoid surgery in most cases

Andrew M. Kaunitz, MD, NCMP; Deanna C. McCullough, MD; and Erin H. Burnett, MD

IN THIS ARTICLE

CASE 1 Multiparous woman presents with heavy regular menses

Over the past several years, a 34-year-old woman has noted increasing intensity and duration of menstrual flow, which now persists for 8 days and includes clots "the size of quarters" and soaks a pad within 1 hour. Sometimes she misses or leaves work on her heaviest days of flow. She reports that menstrual cramps prior to and during flow are increasingly bothersome and do not respond adequately to ibuprofen. She intermittently uses condoms for contraception. She does not wish to be pregnant currently; however, she recently entered into a new relationship and may wish to conceive in the future.

On bimanual examination, the uterus appears bulky. Her hemoglobin is 10.9 g/dL with low mean corpuscular volume and a serum ferritin level indicating iron depletion. Pelvic ultrasonography suggests uterine adenomyosis; no fibroids are imaged (**FIGURE 1**).

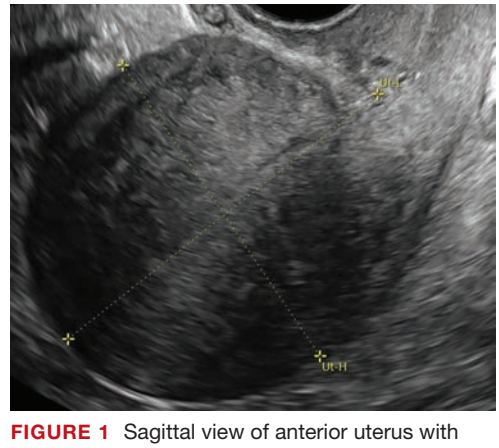

FIGURE 1 Sagittal view of anterior uterus with hyperechoic changes extending anteriorly and posteriorly from the endometrial echo, suggesting adenomyosis. *Image courtesy of Andrew Kaunitz.*

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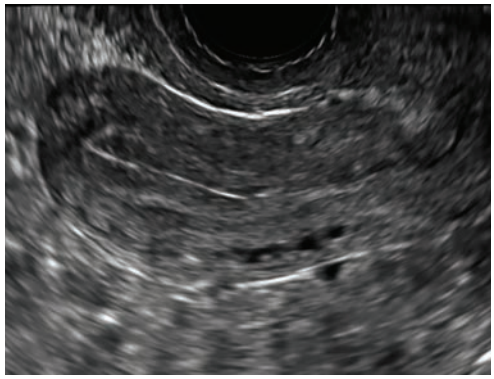

FIGURE 2 Sagittal view of anterior uterus with multiplanar ("trilaminar") endometrium, consistent with proliferative changes. *Image courtesy of Andrew Kaunitz.*

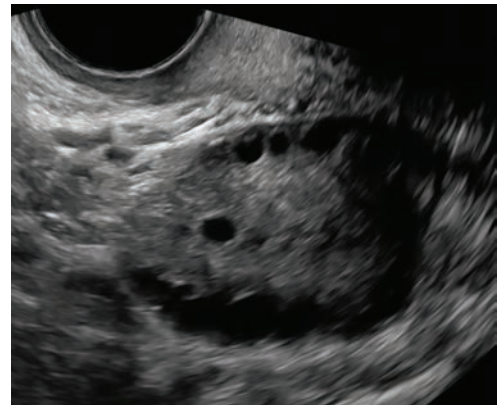

FIGURE 3 Ovary with numerous crowded-appearing cortical follicles, consistent with PCOS. *Image courtesy of Andrew Kaunitz.*

You advise the patient to take ferrous sulfate 325 mg every other day. After discussion with the patient regarding different treatment options, she chooses to proceed with placement of a 52-mg levonorgestrel (LNG) intrauterine device (IUD; Mirena or Liletta).

CASE 2 Older adolescent presents with irregular bleeding

A 19-year-old patient reports approximately 6 bleeding episodes each year. She reports the duration of her bleeding as variable, and sometimes the bleeding is heavy with small clots passed. She has been previously diagnosed with polycystic ovary syndrome (PCOS). Combination estrogen-progestin oral contraceptives have been prescribed several times in the past, but she always has discontinued them due to nausea. The patient is in a same-sex relationship and does not anticipate being sexually active with a male. She reports having to shave her mustache and chin twice weekly for the past 1 to 2 years.

On physical examination, the patient is obese (body mass index [BMI], 32 kg/m^2), facial acne and hirsutism are present, and hair extends from the mons toward the umbilicus. Bimanual examination reveals a normal size, mobile, nontender uterus without obvious adnexal pathology. Pelvic ultrasonography demonstrates a normal-appearing uterus with multiplanar endometrium (consistent with proliferative changes) (**FIGURE 2**). Ovarian imaging demonstrates ≥12 follicles per image (**FIGURE 3**).

After reviewing various treatment options, you prescribe oral medroxyprogesterone acetate 20 mg (two 10-mg tablets) daily in a continuous fashion. You counsel her that she should not be surprised or concerned if frequent or even continuous bleeding occurs initially, and that she should continue this medication despite the occurrence of such.

About one-third of all women experience abnormal uterine bleeding (AUB) sometime during their lifetime and AUB can impair quality of life.[1] Surgical management, including hysterectomy and endometrial ablation, plays an important role in the management of AUB in patients who do not desire future pregnancies. However, many cases of AUB occur in women who may not have completed childbearing or in women who prefer to avoid surgery.[2] AUB can be managed effectively medically in most cases.[1] Accordingly, in this review, we focus on nonsurgical management of AUB.

Because previously used terms, including menorrhagia and meno-metrorrhagia were inconsistently defined and confusing, the International Federation of Gynecology and Obstetrics introduced updated terminology in 2011 to better describe and characterize AUB in nonpregnant women. Heavy menstrual bleeding (HMB) refers to ovulatory (cyclic) bleeding that is more than 8 days' duration, or sufficiently heavy to impair a woman's quality of life. HMB is a

FAST TRACK

Although surgical options are important for managing AUB, heavy bleeding occurs in many women who have not completed childbearing or in those who prefer medical management

pattern of AUB distinct from the irregular bleeding pattern typically caused by ovulatory dysfunction (AUB-O).[1]

Clinical evaluation

Obtain menstrual history. In addition to a medical, surgical, and gynecologic history, a thorough menstrual history should be obtained to further characterize the patient's bleeding pattern. In contrast to the cyclical or ovulatory bleeding seen with HMB, bleeding associated with inconsistent ovulation (AUB-O) is unpredictable or irregular, and is commonly associated with PCOS. AUB-O is also encountered in recently menarchal girls (secondary to immaturity of the hypothalamic-pituitary-gonadal axis) and in those who are perimenopausal. In addition, medications that can induce hyperprolactinemia (such as certain antipsychotics) can cause AUB-O.

Evaluate for all sources of bleeding. Be sure to evaluate for extrauterine causes of bleeding, including the cervix, vagina, vulva, or the urinary or gastrointestinal tracts for bleeding. Intermenstrual bleeding occurring between normal regular menses may be caused by an endometrial polyp, submucosal fibroid, endometritis, or an IUD. The patient report of postcoital bleeding suggests that cervical disease (cervicitis, polyp, or malignancy) may be present. Uterine leiomyoma or adenomyosis represent common causes of HMB. However, HMB also may be caused by a copper IUD, coagulation disorders (including von Willebrand disease), or use of anticoagulant medications. Hormonal contraceptives also can cause irregular bleeding.

Perform a pelvic examination and measure vital signs. The presence of fever suggests the possible presence of pelvic inflammatory disease (PID), while orthostatic hypotension raises the possibility of hypovolemia. When vaginal speculum examination is performed, a cervical cause of abnormal bleeding may be noted. The presence of fresh or old blood or finding clots in the vaginal vault or at the cervical os are all consistent with AUB. A bimanual examination that reveals an enlarged or lobular uterus suggests leiomyoma or adenomyosis. Cervical or adnexal tenderness is often noted in women with PID, which itself may be associated with endometritis. The presence of hyperandrogenic signs on physical examination (eg, acne, hirsutism, or clitoromegaly) suggests PCOS. The finding of galactorrhea suggests that hyperprolactinemia may be present.

FAST TRACK

For women with HMB, screen for iron deficiency by obtaining serum ferritin levels

Laboratory assessment

Test for pregnancy, cervical disease, and sexually transmitted infection when appropriate. Pregnancy testing is appropriate for women with AUB aged 55 years or younger. If patients with AUB are not up to date with normal cervical cancer screening results, cervical cytology and/or human papillomavirus testing should be performed. Testing for *Chlamydia trachomatis, Neisseria gonorrhoeae,* and *Trichomonas vaginalis* should be performed in patients:

- younger than 25 years
- when the history indicates new or multiple sexual partners, or
- when vaginal discharge, cervicitis, cervical motion, or adnexal tenderness is present.

Obtain a complete blood count and serum ferritin levels. In women presenting with HMB, iron depletion and iron deficiency anemia are common. The finding of leukocytosis raises the possibility of PID or postpartum endometritis. In women with presumptive AUB-O, checking the levels of thyroid-stimulating hormone, free T4, and prolactin should be performed.

Screen for a hemostasis disorder. Women with excessive menstrual bleeding should be clinically screened for an underlying disorder of hemostasis (**TABLE 1**).[3] When a hemostasis disorder is suspected, initial laboratory evaluation includes a partial thromboplastin time, prothrombin time, activated partial thromboplastin time, and fibrinogen. Women who have a positive clinical screen for a possible bleeding disorder or abnormal initial laboratory test results for disorders of hemostasis should undergo further labora-

tory evaluation, including von Willebrand factor antigen, ristocetin cofactor assay, and factor VIII. Consultation with a hematologist should be considered in these cases.

Perform endometrial biopsy when indicated

After excluding pregnancy, endometrial biopsy (through pipelle biospy or brush sampling; **FIGURE 4**) should be performed in women with AUB who are at increased risk for endometrial neoplasia. The prevalence of endometrial neoplasia is substantially higher among women ≥45 years of age[4] and among patients with AUB who are also obese (BMI, ≥30 kg/m^2).[5] In addition, AUB patients with unopposed estrogen exposure (presumed anovulation/PCOS), as well as those with persistent AUB or failed medical management, should undergo endometrial biopsy.[6]

Utilize transvaginal ultrasonography

Transvaginal ultrasonography is often useful in the evaluation of patients with AUB, as it may identify uterine fibroids or adenomyosis, suggest intracavitary pathology (such as an endometrial polyp or submucosal fibroid), or raise the possibility of PCOS. In virginal patients or those in whom vaginal ultrasound is not appropriate, abdominal pelvic ultrasonography represents appropriate imaging. If unenhanced ultrasound suggests endometrial polyps or fibroids within the endometrial cavity, an office-based saline infusion sonogram (sonohysterogram) (**FIGURE 5**) or hysteroscopy should be performed. Targeted endometrial sampling and biopsy of intracavitary pathology can be performed at the time of hysteroscopy.

TABLE 1 **Clinical screening for an underlying disorder of hemostasis in the patient with excessive menstrual bleeding**[3]

Initial screening should be structured by the medical history. A positive screening result[a] comprises the following circumstances:

- Heavy menstrual bleeding since menarche
- One of the following conditions:
  - —Postpartum hemorrhage
  - —Surgery-related bleeding
  - —Bleeding associated with dental work
- Two or more of the following conditions:
  - —Bruising, 1 to 2 times per month
  - —Epistaxis, 1 to 2 times per month
  - —Frequent gum bleeding
  - —Family history of bleeding symptoms

[a]Patients with a positive screening result should be considered for further evaluation, including consultation with a hematologist and testing for von Willebrand factor and ristocetin cofactor.

Treatment

When HMB impairs quality of life, is bothersome to the patient, or results in anemia, treatment is appropriate. Although bleeding episodes in women with AUB-O may be infrequent (as with Case 2), treatment prevents heavy or prolonged bleeding episodes as well as endometrial neoplasia that may otherwise occur in anovulatory women.

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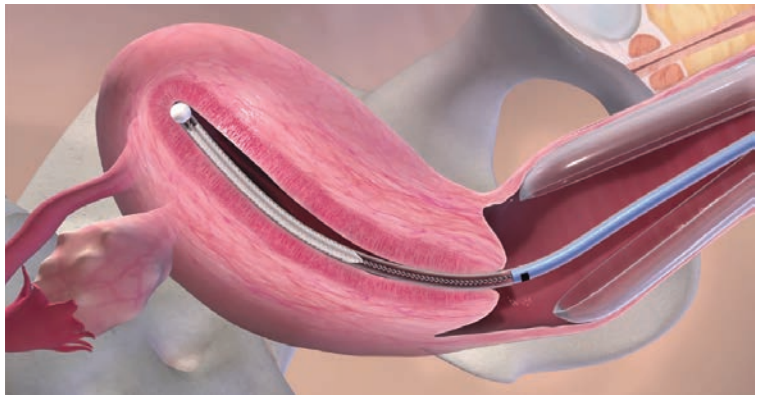

FIGURE 4 Endometrial brush sampling.
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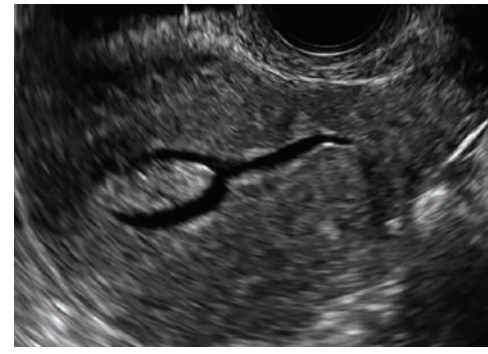

FIGURE 5 Sagittal view of uterus with endometrial cavity distended by saline (sonohysterogram or saline-infusion sonogram), demonstrating fundal endometrial polyp. *Image courtesy of Andrew Kaunitz.*

CONTINUED FROM PAGE 33

TABLE 2 Medical treatment options for management of abnormal uterine bleeding in reproductive-age women[7-14]

- Combination estrogen-progestin contraceptives (oral, vaginal ring, transdermal)
- If use of combination contraceptives are not appropriate due to cardiovascular risk factors, consider continuous (off-label) oral menopausal estrogen-progestin formulations, or oral high-dose progestin therapy:
  - —ethinyl estradiol 5 µg + norethindrone acetate 1 mg (Jinteli 1/5 and other generics)
  - —estradiol 1 mg + norethindrone acetate 0.5 mg (Mimvey and other generics)
- High-dose oral progestin therapy (in contrast to package labeling, continuous therapy preferred to cyclical therapy):
  - —norethindrone acetate 5-mg tablets once daily
  - —medroxyprogesterone acetate 10-mg tablets 1–3 tablets daily
- Levonorgestrel 52 mg IUD (Mirena or Liletta)
- Off-label use of nonsteroidal anti-inflammatory drugs daily for 5 days beginning at the onset of menstrual flow
- Tranexamic acid two 650-mg tablets 3 times daily for up to 5 days during menstrual flow

Many women with AUB can be managed medically. However, treatment choices will vary with respect to the patient's desire for future fertility, medical comorbidities, personal preferences, and financial barriers. While many women may prefer outpatient medical management (**TABLE 2**),[7-14] others might desire surgical therapy, including endometrial ablation or hysterectomy.

Oral contraceptives

Combination estrogen-progestin oral contraceptives represent appropriate initial therapy for many women in the reproductive-age group with AUB, whether women have HMB or AUB-O. However, contraceptive doses of estrogen are not appropriate for some women with risk factors for cardiovascular disease, including those who smoke cigarettes and are age ≥35 years or those who have hypertension (**TABLE 3**).[15,16]

Menopausal dosages of HT

If use of contraceptive doses of estrogen is not appropriate, continuous off-label use of menopausal combination formulations (physiologic dosage) of hormonal therapy (HT; ie, lower doses of estrogen than contraceptives) may be effective in reducing or eliminating AUB. Options for menopausal combination formulations include generic ethinyl estradiol 5 µg/norethindrone acetate 1 mg or estradiol 1 mg/norethindrone acetate 0.5 mg.[7] High-dose oral progestin therapy (norethindrone acetate 5 mg tablet once daily or medroxyprogesterone acetate 10 mg tablets 1–3 times daily) also can be used when combination contraceptives are contraindicated and may be more effective than lower-dose combination formulations.

Package labeling, as well as some guidelines, indicate that oral progestins used to treat AUB should be taken cyclically.[8] However, continuous daily use is easier for many patients and may be more effective in reducing bleeding. Accordingly, we counsel patients with AUB who are using progestins and who do not wish to conceive to take these medications continuously. High-dose oral progestin therapy may cause bloating, dysphoria, and increased appetite/weight gain. Women initiating hormonal management (including the progestin IUDs detailed below) for AUB should be counseled that irregular or even continuous light bleeding/spotting is common initially, but this bleeding pattern typically decreases with continued use.

IUDs

The LNG 52 mg IUD (Mirena or Liletta) effectively treats HMB, reducing bleeding in a manner comparable to that of endometrial ablation.[9,10] The Mirena IUD is approved for treatment of HMB in women desiring intrauterine contraception. In contrast to oral medications, use of progestin IUDs does not involve daily administration and may represent an attractive option for women with HMB who would like to avoid surgery or preserve fertility. With ongoing use, continuous oral or intrauterine hormonal management may result in amenorrhea in some women with AUB.

When the LNG 52 mg IUD is used to treat HMB, the menstrual suppression impact

may begin to attenuate after approximately 4 years of use; in this setting, replacing the IUD often restores effective menstrual suppression.[11] The LNG 52 mg IUD effectively suppresses menses in women with coagulation disorders; if menstrual suppression with the progestin IUD is not adequate in this setting, it may be appropriate to add an oral combination estrogen-progestin contraceptive or high-dose oral progestin.[11,12]

NSAIDs and tranexamic acid

Off-label use of nonsteroidal anti-inflammatory drugs (naproxen 500–1,000 mg daily for 5 days beginning at the onset of menstrual flow or tranexamic acid two 650-mg tablets 3 times daily for up to 5 days during episodes of heavy flow) can suppress HMB and is useful for women who prefer to avoid or have contraindications to hormonal treatments.[13,14] Unfortunately, these agents are not as effective as hormonal management in treating AUB.

Iron supplementation is often needed

Iron depletion commonly results from HMB, often resulting in iron deficiency anemia. When iron depletion (readily identified by checking a serum ferritin level) or iron deficiency anemia is identified, iron supplementation should be recommended. Every-other-day administration of iron supplements maximizes iron absorption while minimizing the adverse effects of unabsorbed iron, such as nausea. Sixty mg of elemental iron (ferrous sulfate 325 mg) administered every other day represents an inexpensive and effective treatment for iron deficiency/anemia.[17] In patients who cannot tolerate oral iron supplementation or for those in whom oral therapy is not appropriate or effective, newer intravenous iron formulations are safe and effective.[18]

CASE 1 Follow-up

The patient noted marked improvement in her menstrual cramps following LNG-containing IUD placement. Although she also reported that she no longer experienced heavy menstrual flow or cramps, she was bothered by frequent, unpredictable light bleeding/spotting. You prescribed norethindrone acetate (NETA) 5-mg tablet orally once daily, to be used in addition to her IUD. After using the IUD with concomitant NETA for 2 months' duration, she noted that her bleeding/spotting almost completely resolved; however, she did report feeling irritable with use of the progestin tablets. She subsequently stopped the NETA tablets and, after 6 months of additional follow-up, reported only minimal spotting and no cramps.

At this later follow-up visit, you noted that her hemoglobin level increased to 12.6 g/dL, and the ferritin level no longer indicated iron depletion. After the IUD had been in place for 4 years, she reported that she was beginning to experience frequent light bleeding again. A follow-up vaginal sonogram noted a well-positioned IUD,

TABLE 3 Cardiovascular-related contraindications[a] to combination estrogen-progestin contraceptives[b,15,16]

- History of deep vein thrombosis (DVT)/pulmonary embolism (PE) or acute DVT/PE
- Major surgery with prolonged immobilization
- Diabetes:
  - —Nephropathy/retinopathy/neuropathy present
  - —Other vascular disease or diabetes of >20 years duration
- Migraines with aura
- Hypertension
- Ischemic heart disease (current or history of)
- Multiple risk factors for cardiovascular disease (older age, smoking, diabetes, hyperlipidemia, and hypertension)
- Peripartum cardiomyopathy
- Smoking (age ≥35)
- History of stroke
- Systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies
- Thrombogenic mutations
- Valvular heart disease that is complicated:
  - —Pulmonary hypertension, risk for atrial fibrillation, history of subacute bacterial endocarditis

[a]All listed contraindications are associated with Category 3 (Theoretic or proven risks of specific contraceptive use outweigh the advantages) or Category 4 (Unacceptable health risks [specific contraceptive method not to be used]) in the US Medical Eligibility Criteria for Contraceptive Use, 2016. This information is also available in a free app (CDC Contraception 2016).

[b]Oral contraceptives, ethinyl estradiol etonogestrel vaginal ring, ethinyl estradiol norelgestromin patch.

there was no suggestion of intracavitary pathology, and adenomyosis continued to be imaged. She underwent IUD removal and placement of a new LNG 52 mg IUD. This resulted in marked reduction in her bleeding.

CASE 2 Follow-up

Two weeks after beginning continuous oral progestin therapy, the patient called reporting frequent irregular bleeding. She was reassured that this was not unexpected and encouraged to continue oral progestin therapy. During a 3-month follow-up visit, the patient noted little, if any, bleeding over the previous 2 months and was pleased with this result. She continued to note acne and hirsutism and asked about the possibility of adding spironolactone to her oral progestin regimen. ●

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Hysterectomy in patients with history of prior cesarean delivery: A reverse dissection technique for vesicouterine adhesions

Vesicouterine adhesions resulting from prior CDs or other surgeries can distort the pelvic anatomy and present challenges during laparoscopic hysterectomy. These experts describe a dissection technique that creates a "new" space and permits safe separation of the bladder from the uterus and cervix, reducing the risk of injury to adjacent structures.

Camran Nezhat, MD; Mailinh Vu, MD; Nataliya Vang, MD; Edzhem Tombash, MS3; and Azadeh Nezhat, MD

IN THIS ARTICLE

Minimally invasive surgical techniques, which have revolutionized modern-day surgery, are the current standard of care for benign hysterectomies.[1-4] Many surgeons use a video-laparoscopic approach, with or without robotic assistance, to perform a hysterectomy. The development of a bladder flap or vesicovaginal surgical space is a critical step for mobilizing the bladder. When properly performed, it allows for appropriate closure of the vaginal cuff while mitigating the risk of urinary bladder damage.

In patients with no prior pelvic surgeries, this vesicovaginal anatomic space is typically developed with ease. However, in patients who have had prior cesarean deliveries (CDs), the presence of vesicouterine adhesions could make this step significantly more challenging. As a result, the risk of bladder injury is higher.[5-8]

With the current tide of cesarean birth rates approaching 33% on a national scale, the presence of vesicouterine adhesions is commonly encountered.[9] These adhesions can distort the anatomy and thereby create more difficult dissections and increase operative time, conversion to laparotomy, and inadvertent cystotomy. Such a challenge also presents an increased risk of injuring adjacent structures.

In this article, we describe an effective method of dissection that is especially useful in the setting of prior CDs. This method involves developing a surgical space lateral and caudal to the vesicovaginal space with subsequent reverse caudal-to-cephalad dissection.

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Steps in operative planning

Preoperative evaluation. A thorough preoperative evaluation should be performed for patients planning to undergo a laparoscopic hysterectomy. This includes obtaining details of their medical and surgical history. Access to prior surgical records may help to facilitate planning of the surgical approach. Previous pelvic surgery, such as CD, anterior myomectomy, cesarean scar defect repair, endometriosis treatment, or exploratory laparotomy, may predispose these patients to develop adhesions in the anterior cul-de-sac. Our method of reverse vesicouterine fold dissection can be particularly efficacious in these settings.

Surgical preparation and laparoscopic port placement. In the operative suite, the patient is placed under general anesthesia and positioned in the dorsal lithotomy position.[10] Sterile prep and drapes are used in the standard fashion. A urinary catheter is inserted to maintain a decompressed bladder. A uterine manipulator is inserted with good placement ensured.

Per our practice, we introduce laparoscopic ports in 4 locations. The first incision is made in the umbilicus for the introduction of a 10-mm laparoscope. Three subsequent 5-mm incisions are made in the left and right lower lateral quadrants and medially at the level of the suprapubic region.[10] Upon laparoscopic entry, we perform a comprehensive survey of the abdominopelvic cavity. Adequate mobility of the uterus is confirmed.[11] Any posterior uterine adhesions or endometriosis are treated appropriately.[12]

First step in the surgical technique: Lateral dissection

We proceed by first desiccating and cutting the round ligament laterally near the inguinal ligament. This technique is carried forward in a caudal direction as the areolar tissue near the obliterated umbilical artery is expanded by the pneumoperitoneum. With a vessel sealing-cutting device, we address the attachments to the adnexa. If the ovaries are to be retained, the utero-ovarian ligament is dessicated and cut. If an oophorectomy is indicated, the infundibulopelvic ligament is dessicated and cut.

Using the tip of the vessel sealing-cutting device, the space between the anterior and posterior leaves of the broad ligament is developed and opened. A grasping forceps is then used to elevate the anterior leaf of the broad ligament and maintain medial traction. A space parallel and lateral to the cervix and vagina is then created with blunt dissection.

The inferior and medial direction of this dissection is paramount to avoid injury to nearby structures in the pelvic sidewall. Gradually, this will lead to the identification of the vesciovaginal ligament and then the vesicocervical ligament. The development of these spaces allows for the lateral and inferior displacement of the ureter. These maneuvers can mitigate ureter injury by pushing it away from the planes of dissection during the hysterectomy.

Continued traction is maintained by keeping the medial aspect of the anterior leaf of the broad ligament intact. However, the posterior leaf is dissected next, which further lateralizes the ureter. Now, with the uterine vessels fully exposed, they are thoroughly dessicated and ligated. The same procedure is then performed on the contralateral side.[11] (See the box above for links to videos that demonstrate the techniques described here.)

CONTINUED ON PAGE 40

These videos demonstrate the reverse vesicouterine fold dissection technique

From the Center for Special Minimally Invasive and Robotic Surgery

https://youtu.be/wgGssnd1JAo
Reverse vesicouterine fold dissection for total laparoscopic hysterectomy

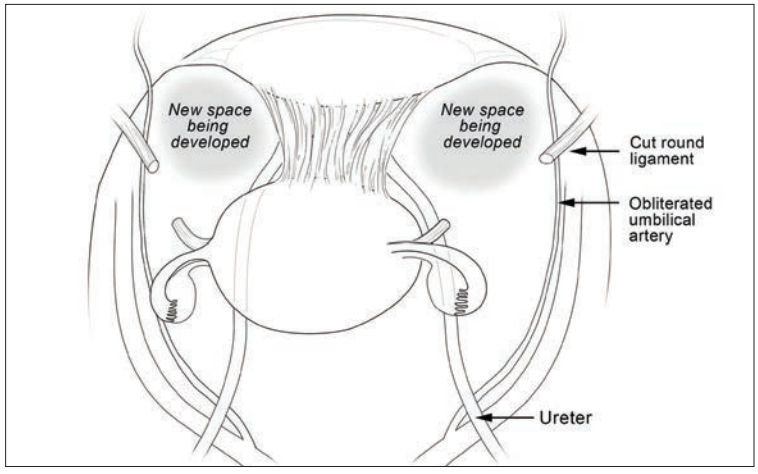
- Case 1: TLH with development of the "new space": The technique with prior C-section
- Case 2: A straightforward case: Dysmenorrhea and menorrhagia
- Case 3: History of multiple C-sections with adhesions and fibroids

https://youtu.be/6vHamfPZhdY
Reverse vesicouterine fold dissection for total laparoscopic hysterectomy after prior cesarean delivery

Hysterectomy in patients with history of prior CD

CONTINUED FROM PAGE 39

FIGURE 1 New space created by the reverse vesicouterine fold dissection technique



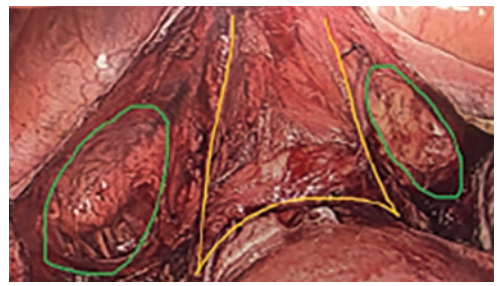
Creation of a "new" space in the vesicovaginal space, using a blunt sweeping motion from an inferior-to-superior direction, facilitates hysterectomy in patients with anterior cul-de-sac adhesions from prior cesarean deliveries or other surgeries.

Creating the "new" space

In the "new" space that was partially developed during the lateral dissection, blunt dissection is continued, using a sweeping motion from an inferior-to-superior direction, to extend this avascular space. This is performed bilaterally until both sides are connected from the inferior aspect of the vesicouterine adhesions, if present. This thorough dissection creates what we refer to as a "new" space[11] (**FIGURE 1**).

Medially, the new space is bordered by the vesicocervical-vaginal ligament, also known as the bladder pillar. Its distal landmark is the bladder. The remaining intact anterior leaf of the broad ligament lies adjacent to the space anteriorly. The inner aspect of the obliterated umbilical artery neighbors it laterally. Lastly, the vesicovaginal plane's posterior margin is the parametrium, which is the region where the ureter courses into the bladder. The paravesical space lies lateral to the obliterated umbilical ligament.

FIGURE 2 Vesicocervical space boundaries (yellow) and "new" space boundaries (green)



Visualization of this new space is made possible in the laparoscopic setting. The pneumoperitoneum allows for better demarcation of the space. Additionally, laparoscopic views of the anatomic spaces differ from those of the laparotomy view because of the magnification and the insufflation of carbon dioxide gas in the spaces.[13,14] In our experience, approaching the surgery from the "new" space could significantly decrease the risk of genitourinary injuries in patients with anterior cul-de-sac adhesions (**FIGURE 2**).

Using the reverse vesicouterine fold dissection technique

Among patients with prior CDs, adhesions often are at the level of or superior to the prior CD scar. By creating the new space, safe dissection from a previously untouched area can be accomplished and injury to the urinary bladder can be avoided.

The reverse vesicouterine fold dissection can be performed from this space. Using the previously described blunt sweeping motion from an inferior-to-superior direction, the vesicovaginal and vesicocervical space is further developed from an unscarred plane. This will separate the lowest portion of the bladder from the vagina, cervix, and uterus in a safe manner. Similar to the technique performed during a vaginal hysterectomy, this reverse motion of developing the bladder flap avoids erroneous and blind dissection through the vesicouterine adhesions (**FIGURES 3–5**).

Once the bladder adhesions are well delineated and separated from the uterus by the reverse vesicouterine fold dissection technique, it is safe to proceed with complete bladder mobilization. Sharp dissection can be used to dissect the remaining scarred

ILLUSTRATION: MARCIA HARTSOCK FOR OBG MANAGEMENT

FIGURE 3 Laparoscopic view of the dense bladder adhesions to the uterine corpus prior to dissection

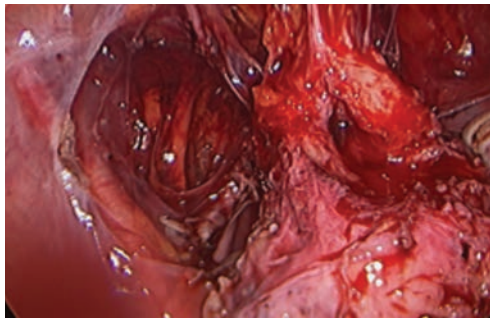
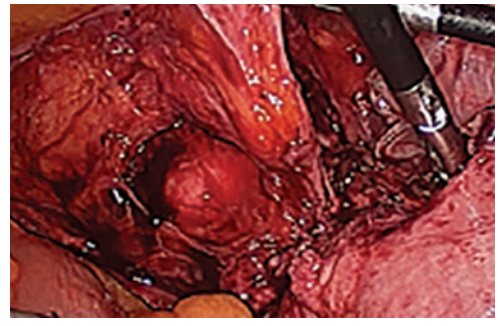


FIGURE 4 Laparoscopic view demonstrating blunt dissection to create the "new" space



bladder at its most superior attachments. Avoid the use of thermal energy to prevent heat injury to the bladder. Carefully dissect the bladder adhesions from the cervicouterine junction. Additional inferior bladder mobilization should be performed up to 3 cm past the leading edge of the cervicovaginal junction to ensure sufficient vaginal tissue for cuff closure. Note that the bladder pillars occasionally may be trapped inside a CD scar. This surgical technique could make it easier to release the pillars from inside the adhesions and penetrating into the scar.[15]

Completing the surgery

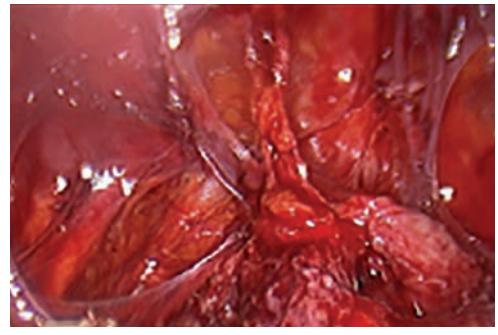
Once the bladder is freely mobilized and all adhesions have been dissected, the cervix is circumferentially amputated using monopolar cautery. The vaginal cuff can then be closed from either a laparoscopic or vaginal approach using polyglactin 910 (0-Vicryl) or barbed (V-Loc) suture in a running or interrupted fashion. Our practice uses a 1.5-cm margin depth with each suture. At the end of the surgery, routine cystoscopy is performed to verify distal ureteral patency.[16] Postoperatively, we manage these patients using a fast-track, or enhanced recovery, model.[17]

An effective technique in challenging situations

Genitourinary injury is a common complication of hysterectomy.[18] The proximity of the bladder and ureters to the field of dissection during a hysterectomy can be especially challenging when the anatomy is distorted by adhesion formation from prior surgeries. One study demonstrated a 1.3% incidence of urinary tract injuries during laparoscopic hysterectomy.[6] This included 0.54% ureteral injuries, 0.71% urinary bladder injuries, and 0.06% combined bladder and ureteral injuries.[6] Particularly among patients with a prior CD, the risk of bladder injury can be significantly heightened.[18]

The reverse vesicouterine fold dissection technique that we described offers multiple benefits. By starting the procedure from an untouched and avascular plane, dissection into the plane of the prior adhesions can be circumvented; thus, bleeding is limited and injury to the bladder and ureters is avoided

FIGURE 5 Laparoscopic view showing the skeletonized bladder adhesions



FAST TRACK

By starting the procedure from an untouched, avascular plane, dissection into the plane of the prior adhesions can be circumvented. Thus, bleeding is limited and injury to the bladder and ureters is avoided or minimized.

Hysterectomy in patients with history of prior CD

or minimized. By using blunt and sharp dissection, thermal injury and delayed necrosis can be mitigated. Finally, with bladder mobilization well below the colpotomy site, more adequate vaginal tissue is free to be incorporated into the vaginal cuff closure, thereby limiting the risk of cuff dehiscence.[16]

While we have found this technique effective for patients with prior cesarean surgeries, it also may be applied to any patient who has a scarred anterior cul-de-sac. This could include patients with prior myomectomy, cesarean scar defect, or endometriosis. Despite the technique being a safeguard against bladder injury, surgeons must still use care in developing the spaces to avoid ureteral injury, especially in a setting of distorted anatomy. ●

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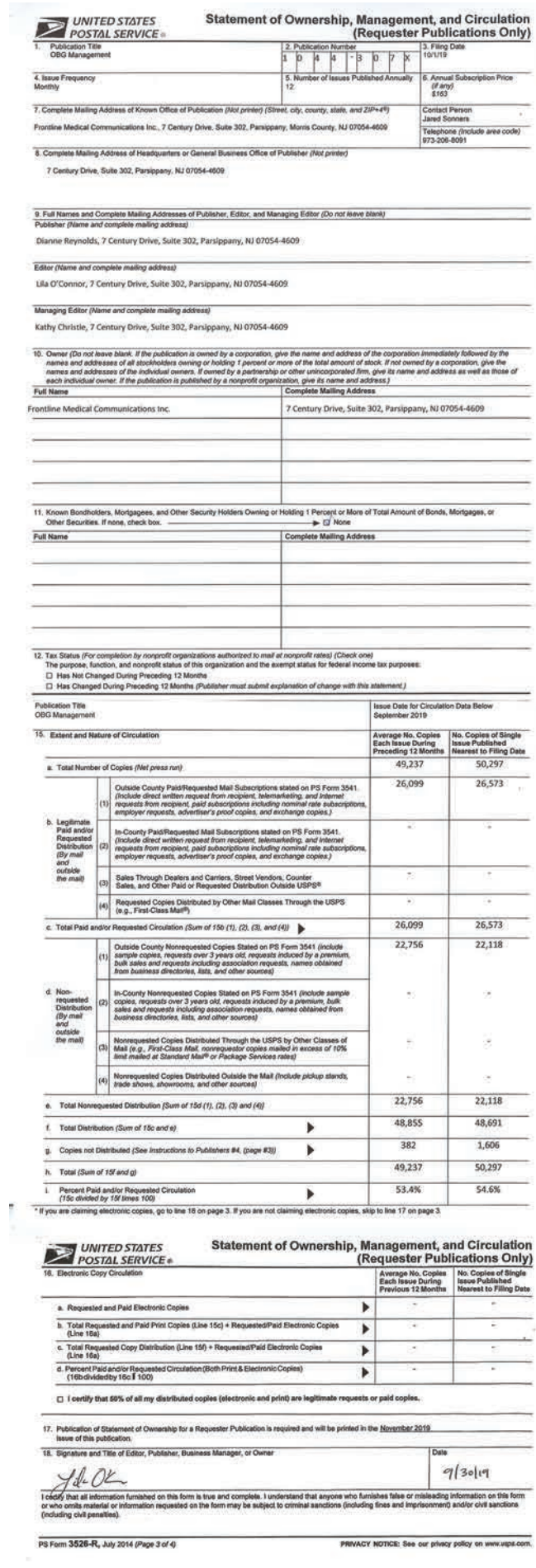

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a. Total Number of Copies (Net press run)			49,237	50,297
b. Legitimate Paid and/or Requested Distribution (By mail and outside the mail)	(1)	Outside County Paid/Requested Mail Subscriptions stated on PS Form 3541. (Include direct written request from recipient, telemarketing, and Internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)	26,099	26,573
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f. Total Distribution (Sum of 15c and e) ▶			48,855	48,691
g. Copies not Distributed (See Instructions to Publishers #4, (page #3)) ▶			382	1,606
h. Total (Sum of 15f and g)			49,237	50,297
i. Percent Paid and/or Requested Circulation (15c divided by 15f times 100) ▶			53.4%	54.6%

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Three free apps for urogynecology providers

These informational and clinical decision-making apps provide position statements, risk calculators, and interactive animations

Katherine T. Chen, MD, MPH

IN THIS ARTICLE

Details on recommended apps
page 45

Thousands of medical apps are available for smart mobile devices; however, identifying accurate and high-quality apps poses a challenge to health care providers. In the field of urogynecology, also known as female pelvic medicine and reconstructive surgery (FPMRS), the authors of a recent study identified and rated a number of apps for use by urogynecologists.[1]

The 3 apps featured here are all free and are both informational and clinical decision-making apps.

Informational apps include one or more of the following datasets in a given condition: epidemiology, etiology/pathophysiology, histology/pathology, clinical presentation, treatment, follow-up care, prevention, and/or prognosis.

Clinical decision-making apps may have the following functionalities within the app: clinical decision support systems, clinical treatment guidelines, disease diagnosis aids, differential diagnosis aids, medical calculators, laboratory test ordering, laboratory test interpretation, and/or medical exams.

The **TABLE** details the features of these recommended apps based on a shortened version of the APPLICATIONS scoring system, APPLI (app comprehensiveness, price, platform, literature used, and important special features).[2] I hope urogynecologists view these apps as innovative educational resources that provide quick medical knowledge and pelvic floor patient education. ●

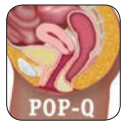
Dr. Chen is Professor of Obstetrics, Gynecology, and Reproductive Science and Medical Education, Vice-Chair of Ob-Gyn Education for the Mount Sinai Health System, Icahn School of Medicine, Mount Sinai, New York, New York. She is an OBG MANAGEMENT Contributing Editor.

The author reports being an advisory board member and receiving royalties from UpToDate, Inc.

References

1. Wallace SL, Mehta S, Farag S, et al. In search of mobile applications for urogynecology providers. *Female Pelvic Med Reconstr Surg*. 2018. doi:10.1097/SPV.0000000000000580.
2. Chyjek K, Farag S, Chen KT. Rating pregnancy wheel applications using the APPLICATIONS scoring system. *Obstet Gynecol*. 2015;125:1478-1483.

TABLE Recommended FPMRS apps

App	App comprehensiveness	Price	Platform	Literature used	Important special features
 **AUGS NOW** by Results Direct iTunes only: https://apps.apple.com/br/app/augs-now/id1038504673?l=en	• Informational (all) • Clinical decision making (clinical treatment guidelines, disease diagnosis aids, medical calculator)	Free	iTunes	Developed by the American Urogynecologic Society (AUGS)	• Guidelines and position statements • Risk calculator for de novo postoperative stress urinary incontinence after surgery for pelvic organ prolapse • Study tool with question of the day
 **AUGS POP-Q** by the American Urogynecologic Society iTunes only: https://apps.apple.com/us/app/augs-pop-q/id1214333063	• Informational (clinical presentation, diagnosis, treatment) • Clinical decision making (clinical decision support systems, disease diagnosis aids, medical calculator, medical exams)	Free	iTunes	Developed in consultation with Patrick Culligan, MD	• Interactive POP-Q assessment guide • Sample image library • Stress urinary incontinence animations
 **POP-Q** by Boston Scientific iTunes only: https://apps.apple.com/us/app/pop-q/id471325264	• Informational (clinical presentation, diagnosis, treatment) • Clinical decision making (clinical decision support systems, disease diagnosis aids, medical exams)	Free	iTunes	Developed in consultation with Patrick Culligan, MD	• Images • Interactive disease state animations

Abbreviation: FPMRS, female pelvic medicine and reconstructive surgery.

Coming soon…

- **Update on bone health**
  Steven R. Goldstein, MD
- **Prevention and management of group B streptococcal disease in newborns**
  Patrick Duff, MD
- **Managing eating disorders in pregnancy**
  Gianna Wilkie, MD; Leena Mittal, MD; and Nicole Smith, MD, MPH
- **Update on obstetrics**
  Jaimey Pauli, MD
- **Your patient has dense breasts: What are your next best steps to counsel her?**
  Laila Samiian, MD
- **The One Step test: The better approach for diagnosing gestational diabetes**
  Vincenzo Berghella, MD, and Gabriele Saccone, MD

SCOTUS RECAP

What every ObGyn should know about Supreme Court rulings in the recent term

How has the Supreme Court decided cases involving restrictions on abortion, reimbursements for service for Medicare patients, the statute of limitations for Federal False Claims Acts, pharmaceutical liability, and other important cases of its 2018-2019 term?

Joseph S. Sanfilippo, MD, MBA, and Steven R. Smith, MS, JD

IN THIS ARTICLE

The most recently concluded term of the US Supreme Court, which began on October 1, 2018, yielded a number of decisions of interest to health care professionals and to ObGyns in particular. Although the term was viewed by some observers as less consequential than other recent terms, a review of the cases decided paints a picture of a more important term than some commentators expected.

When the term began, the Court had only 8 justices—1 short of a full bench: Judge Brett Kavanaugh had not yet been confirmed by the Senate. He was confirmed on October 6, by a 50-48 vote, and Justice Kavanaugh immediately joined the Court and began to hear and decide cases.

Dr. Sanfilippo is Professor, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh, and Academic Division Director, Reproductive Endocrinology and Infertility, Magee-Womens Hospital, Pittsburgh, Pennsylvania. He also serves on the OBG MANAGEMENT Board of Editors.

Mr. Smith is Professor Emeritus and Dean Emeritus at California Western School of Law, San Diego, California.

The authors report no financial relationships relevant to this article.

Increasingly, important decisions affect medical practice

From the nature of practice (abortion), to payment for service (Medicare reimbursement), resolution of disputes (arbitration), and fraud and abuse (the federal False Claims Act), the decisions of the Court will have an impact on many areas of medical practice. Organized medicine increasingly has recognized the significance of the work of the Court; nowhere has this been more clearly demonstrated than with *amicus curiae* (friend of the court) briefs filed by medical organizations.

***Amicus curiae* briefs.** These briefs are filed by persons or organizations not a party to a case the Court is hearing. Their legitimate purpose is to inform the Court of 1) special information within the expertise of the *amicus* (or *amici*, plural) or 2) consequences of the decision that might not be apparent from arguments made by the parties to the

case. Sometimes, the Court cites *amicus* briefs for having provided important information about the case.

Filing *amicus* briefs is time-consuming and expensive; organizations do not file them for trivial reasons. Organizations frequently join together to file a joint brief, to share expenses and express to the Court a stronger position.

Three categories of health professionals file *amicus* briefs in ObGyn-related cases:

- Major national organizations, often representing broad interests of health care professions or institutions (the American Medical Association [AMA], the Association of American Medical Colleges, and the American Hospital Association [AHA]), have filed a number of *amicus* briefs over the years.
- Specialty boards increasingly file *amicus* briefs. For example, the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine have filed briefs related to abortion issues.
- In reproductive issues, the American Association of Pro-Life Obstetricians and Gynecologists, the American College of Pediatricians, and the Christian Medical & Dental Associations have been active *amicus* filers—frequently taking positions different than, even inconsistent with, *amicus* briefs filed by major specialty boards.

Amicus briefs filed by medical associations provide strong clues to what is important to clinicians. We have looked at such briefs to help us identify topics and cases from the just-concluded term that can be of particular interest to you.

Surveying the shadow docket. As part of our review of the past term, we also looked at the so-called shadow docket, which includes decisions regarding writs of *certiorari* (which cases it agrees to hear); stays (usually delaying implementation of a law); or denials of stays. (Persuading the Court to hear a case is not easy: It hears approximately 70 cases per year out of as many as 7,000 applications to be heard.)

Abortion ruling

At stake. A number of states recently enacted a variety of provisions that might make an abortion more difficult to obtain. Some of the cases challenging these restrictions are making their way through lower courts, and one day might be argued before the Supreme Court. However, the Court has not (yet) agreed to hear the substance of many new abortion-related provisions.

Box v Planned Parenthood of Indiana and Kentucky, Inc.

The Court decided only 1 abortion restriction case this term.[1] The Indiana law in question included 2 provisions that the Court considered:

Disposal of remains. The law regulated the manner in which abortion providers can dispose of fetal remains (ie, they cannot be treated as "infectious and pathologic waste").

Motivation for seeking abortion. The Indiana law makes it illegal for an abortion provider to perform an abortion when the provider knows that the mother is seeking that abortion "solely" because of the fetus's race, sex, diagnosis of Down syndrome, disability, or related characteristics.

Final rulings. The Court held that the disposal-of-remains provision is constitutional. The provision is "rationally related to the state's interest in proper disposal of fetal remains."[2] Planned Parenthood had not raised the issue of whether the law might impose an undue burden on a woman's right to obtain an abortion, so the Court did not decide that issue.

The Court did not consider the constitutionality of the part of the law proscribing certain reasons for seeking an otherwise legal abortion; instead, it awaits lower courts' review of the issue. Justice Clarence Thomas wrote an extensive concurring opinion suggesting that this law is intended to avoid abortion to achieve eugenic goals.[3]

Key developments from the shadow docket

The Court issued a stay preventing a Louisiana

FAST TRACK

Organizations frequently join together to file a joint amicus brief, to share expenses and express to the Court a stronger position

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Mark D. Walters, MD
Cleveland Clinic

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Michael S. Baggish, MD
St. Helena Hospital

Linda D. Bradley, MD
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Andrew I. Brill, MD
California Pacific Medical Center

Amanda Nickles Fader, MD
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John B. Gebhart, MD, MS
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- Office-Based Gynecologic Procedures

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For complete information and to register please see our website: **PAGS-cme.org**.

PAGS AGENDA

Agenda and faculty is subject to change. Please see website for updates.

WEDNESDAY, DECEMBER 11, 2019

PRE-CONFERENCE WORKSHOPS
(Optional, Separate fee required)

WORKSHOP A 8:30 AM – 12:30 PM
Energy-Based Devices for Hysterectomy and Tissue Extraction Techniques NEW!
Led by: Rosanne M. Kho, MD
4 CME Credits Available

WORKSHOP B 8:30 AM – 12:30 PM
Hands-On Laparoscopic Suturing - The "Vertical Zone" (Simulation Lab)
Led by: Charles H. Koh, MD
4 CME Credits Available

WORKSHOP C 8:30 AM – 5:30 PM
Office-Based Gynecologic Procedures
All day workshop (Includes a morning lecture series and afternoon practicum.)
Led by: Tommaso Falcone, MD
8 CME Credits Available

WORKSHOP D 1:30 PM – 5:30 PM
Technical Aspects of Vaginal Hysterectomy & Cystourethroscopy for the Gynecologist
Led by: Mickey M. Karram, MD
4 CME Credits Available

GENERAL SCIENTIFIC SESSIONS

THURSDAY, DECEMBER 12, 2019

6:45 AM **Registration/Breakfast/Exhibits**

7:50 AM **Course Overview**
Mickey M. Karram, MD

PELVIC ANATOMY

8:00 AM **Pelvic and Abdominal Anatomy from the Laparoscopic Surgeon's View**
Tommaso Falcone, MD

8:40 AM **Anatomic Considerations: Facilitating Vaginal Procedures Safely and Effectively**
Mickey M. Karram, MD

INCONTINENCE AND PROLAPSE SURGERY

9:10 AM **Panel Discussion: Evaluation and Non-Surgical Management of Female Pelvic Floor Disorders: What Every Generalist Should Know**
John B. Gebhart, MD, MS
Mickey M. Karram, MD
Beri M. Ridgeway, MD

9:55 AM **Question and Answer Session**

10:25 AM **Break/Exhibits**

11:25 AM **Surgery for Stress Incontinence and the Future of Synthetic Slings**
Beri M. Ridgeway, MD

12:05 PM **Surgery for Pelvic Organ Prolapse: Do We Need to Perform and Teach More Transvaginal Native Tissue Suture Repairs?**
John B. Gebhart, MD, MS

12:25 PM **Mesh-Augmented Prolapse Repair: Is There Any Role for Vaginal Mesh: Indication and Technique of Sacral Colpopexy**
Beri M. Ridgeway, MD

12:55 PM **Question and Answer Session**

1:10 PM **Lunch**

1:25 PM **Luncheon Symposium**

2:10 PM **Dessert Break/ Exhibits**

THURSDAY'S KEYNOTE LECTURE

2:40 PM **The Evolution of Surgical Procedures Used to Correct Pelvic Organ Prolapse**
Mark D. Walters, MD

BENIGN GYNECOLOGY

3:25 PM **Safe Use of Energy-Based Devices for Gynecologic Surgery**
Andrew I. Brill, MD

3:55 PM **Management of Endometriosis**
Tommaso Falcone, MD

4:40 PM **The Hysteroscopic Treatment of Submucosal Fibroids and Polyps**
Linda D. Bradley, MD

5:10 PM **Question and Answer Session**

FRIDAY, DECEMBER 13, 2019

6:45 AM **Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

HYSTERECTOMY - TECHNIQUE

8:15 AM **The Difficult Vaginal Hysterectomy**
Rosanne M. Kho, MD

8:45 AM **When is it Appropriate to Remove Ovaries at Hysterectomy?**
Amanda Nickles Fader, MD

9:15 AM **Total Laparoscopic Hysterectomy**
Andrew I. Brill, MD

9:45 AM **Break /Exhibits**

10:30 AM **Robotic Hysterectomy**
Javier F. Magrina, MD

11:00 AM **Tissue Extraction Techniques (Morcellation)**
Rosanne M. Kho, MD

11:30 AM **Uterine Preserving Procedures in Patients with Pelvic Organ Prolapse**
Mickey M. Karram, MD
Beri M. Ridgeway, MD

12:00 PM **Enhanced Recovery after Surgery**
Javier F. Magrina, MD

12:30 PM **Question and Answer Session**

1:00 PM **Lunch**

1:15 PM **Luncheon Symposium**

2:00 PM **Dessert Break/Exhibits**

FRIDAY'S KEYNOTE LECTURE

2:30 PM **Techniques to Preserve Level 1 Support at the Time of Vaginal Laparoscopic and Robotic Hysterectomy**
Mark D. Walters, MD

ONCOLOGY FOR THE GENERALIST

3:15 PM **Surgical Management of Pre-Cancer Vulvovaginal Lesions**
Amanda Nickles Fader, MD

4:00 PM **Laparoscopic and Robotic Management of the Adnexal Mass**
Javier F. Magrina, MD

4:45 PM **Spectrum of Vulvovaginal Disorders**
Michael S. Baggish, MD

5:30 PM **Question and Answer Session**

SATURDAY, DECEMBER 14, 2019

6:30 AM **Breakfast**

7:30 AM **Myomectomy: Open to Robotic Approaches**
Tommaso Falcone, MD

8:30 AM **Avoiding and Managing Urogynecologic Complications**
John B. Gebhart, MD, MS
Mickey M. Karram, MD

9:30 AM **Avoiding and Managing Laparoscopic Complications**
Tommaso Falcone, MD

10:30 AM **Break**

10:45 AM **Interesting Case Presentations in Medical Legal**
Michael S. Baggish, MD
Tommaso Falcone, MD

11:30 AM **Surgical Tips for Successful Pelvic Surgery: Video Session**
Surgical Management of Cornual Ectopic & Dermoid Cysts
Tommaso Falcone, MD

Techniques to Suspend the Apex at the Time of Vaginal Surgery
Mickey M. Karram, MD

1:00 PM **Question and Answer Session**

1:15 PM **PAGS Scientific Program Adjournment**

P.E.P. PRACTICE ENHANCEMENT PROGRAM AGENDA (Optional)

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Neil H. Baum, MD
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Author, *The Complete Business Guide to a Successful Medical Practice* and *3-Stages of a Physician's Career*

Faculty
Stephanie Stinchcomb Storck, CPC, CCS-P, ACS-UR

SATURDAY, DECEMBER 14, 2019 Encore at Wynn Las Vegas

2:00 PM **Course Overview**

2:10 PM
- Improving the efficiency and the productivity of the gynecologic practice
- Harnessing social media for the gynecologic practice
- Financial planning for gynecologists

3:30 PM **Break**

3:45 PM
- Coding update for gynecologists
- Numbers you should know
- Mindfulness for doctors
* Physician burnout

5:00 PM **Q and A**

5:30 PM **P.E.P. Adjournment**

PAGS Scientific Faculty

Course Chairs

Tommaso Falcone, MD
Chief of Staff
Chief Academic Officer
Medical Director
Cleveland Clinic London
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
London, UK

Mickey M. Karram, MD
Director of Urogynecology
The Christ Hospital
Volunteer Professor of Ob/Gyn
University of Cincinnati
Cincinnati, Ohio

Special Keynote Speaker

Mark D. Walters, MD
Professor and Vice-Chair of Gynecology
Department of Obstetrics and Gynecology
Cleveland Clinic
Cleveland, Ohio

Faculty

Michael S. Baggish, MD
Professor of Obstetrics and Gynecology
University of California San Francisco
St. Helena, California

Linda D. Bradley, MD
Vice Chair
Obstetrics, Gynecology, and Women's Health Institute
Director
Center for Menstrual Disorders
Professor of Surgery
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Andrew I. Brill, MD
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Cleveland Clinic
Assistant Professor
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Cleveland, Ohio

Optional Workshops

For complete information please see PAGS-CME.org.

Wednesday, December 11, 2019, Encore at Wynn Las Vegas

Optional Hands-on Workshops

PAGS hands-on workshops have limited space available and are selling out quickly! Register Now!

(See PAGS website for complete workshop details.)

WORKSHOP A
ENERGY-BASED DEVICES FOR HYSTERECTOMY AND TISSUE EXTRACTION TECHNIQUES NEW!
4 CME Credits Available
8:30 AM - 12:30 PM
Led by: Rosanne M. Kho, MD
Faculty: Andrew I. Brill, MD;
Keith B. Isaacson, MD

WORKSHOP B
HANDS-ON LAPAROSCOPIC SUTURING - THE "VERTICAL ZONE" (SIMULATION LAB)
4 CME Credits Available
8:30 AM - 12:30 PM
Led by: Charles H. Koh, MD

WORKSHOP C
OFFICE-BASED GYNECOLOGIC PROCEDURES: THE GYNECOLOGIST OF THE FUTURE
FULL-DAY WORKSHOP
8 CME Credits Available
8:30 AM - 5:30 PM
Includes a morning lecture series and afternoon practicum on vulvar/vaginal injections and excisions, ultrasound and hysteroscopy

Led by: Tommaso Falcone, MD
Faculty: Andrew Brill, MD;
Linda D. Bradley, MD; Mark Dassel, MD;
Jeffrey R. Dell, MD; Laura Detti, MD;
Oluwatosin Goje, MD; Keith Isaacson, MD;
Mickey Karram, MD; James M. Shwayder, MD, JD

WORKSHOP D
TECHNICAL ASPECTS OF VAGINAL HYSTERECTOMY & CYSTOURETHROSCOPY FOR THE GYNECOLOGIST
4 CME Credits Available
1:30 PM - 5:30 PM
Led by: Mickey M. Karram, MD
Faculty: Rosanne M. Kho, MD; Doug Miyazaki, MD

Who Should Attend?

The PAGS conference is designed for obstetricians/gynecologists, second, third and fourth-year residents in Ob/Gyn, as well as sub-specialty fellows and advanced practice clinicians. Residents and advanced practice health clinicians are welcome at reduced rates.

ACCREDITATION

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Cincinnati and Global Academy for Medical Education, LLC. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

The University of Cincinnati designates this Live Activity for 20 *AMA PRA Category 1 credits*™ for the conference and (1) 8-hour pre-conference workshops at 8.0 *AMA PRA Category 1 credits*™, (3) 4-hour pre-conference hands-on workshops at 4.0 *AMA PRA Category 1 credits*™ each and (1) post workshop at 3.25 *AMA PRA Category 1 credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

2019

PAGS PELVIC ANATOMY and GYNECOLOGIC SURGERY SYMPOSIUM

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"Enjoy and appreciated attending as have attended twice. Was straightforward and topics covered very well."

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"This is such good educational time. I love how there is something current and relevant everytime I attend (this is my third time)."

"Continue with what you do and that is provide 2 ½ days of excellent information to the average practicing Ob/Gyn."

"This is a fantastic conference year after year! I have travelled from Australia on three occasions to attend."

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8 CME Credits Available
December 11, 2019

SCIENTIFIC SESSIONS
20 CME Credits Available
December 12-14, 2019

Optional **"P.E.P." PRACTICE MANAGEMENT PROGRAM**
3.25 CME Credits Available
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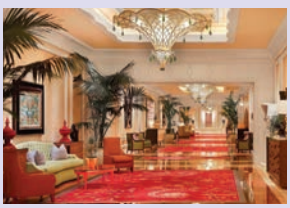
About Our Venue

Encore at Wynn Las Vegas



The 2019 Pelvic Anatomy and Gynecologic Surgery Symposium (PAGS) will take place at the Encore Wynn Las Vegas where we have arranged for a discount room rate of **just $179* a night for PAGS participants.** Subject to availability. To make your reservation, please call (866) 770-7555. You must identify yourself as a Pelvic Anatomy and Gynecologic Surgery Symposium 2019 attendee or reference the block code: 6PAG1219 to receive the discounted rate.

*Plus $25 amenity fee

How to Register for PAGS

Online: www.PAGS-CME.org
Inquiries: PAGS@globalacademycme.com

	Pre-conference	Onsite
PAGS Scientific Program		
■ Physicians	$995	$1095
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■ **Best Buy!** PAGS + P.E.P. Discount Combination Package	$1,395	$1,495
■ **Office-Based Gynecologic Procedures: The Gynecologist of the Future All Day Workshop**	$545	$595
■ **Laparoscopic Suturing Morning Workshop**	$345	$395
■ **Energy-Based Devices for Hysterectomy and Tissue Extraction Techniques**	$345	$395
■ **Vaginal Hysterectomy & Cystourethroscopy Afternoon Workshop**	$395	$445

Cancellation Policy: Full refund less a $50 administrative fee as follows: Cancellations can be made using our online registration system until November 12, 2019. After November 12, 2019 no refunds will be granted. After the refund date, you have two options: you can send someone in your place, or we can mark a credit in the amount you paid minus $50 administration fee, (plus additional $35 administration fee per workshop) to be applied to your registration for next year's conference. Refunds will not be issued to no-shows.

To register and for complete information please see our website: PAGS-cme.org.

statute that requires physicians who perform abortions to have admitting privileges at a nearby hospital from going into effect, pending the outcome of litigation about that law.[4] Four dissenters noted that all 4 physicians who perform abortions in Louisiana have such privileges. Chief Justice Roberts was the fifth vote to grant the stay. This case likely will make its way back to the Court, as will a number of other state laws being adopted. The issue may be back as soon as the term just starting.

The Court is also considering whether to take another Indiana case, Box v Planned Parenthood of Indiana and Kentucky, Inc. (Box II). This case involves an Indiana ultrasonography viewing option as part of the abortion consent process.[5]

The Court declined to hear cases from Louisiana and Kansas in which the states had cut off Medicaid funding to Planned Parenthood. Lower courts had stopped the implementation of those laws.[6] The legal issue was whether private parties, as opposed to the federal government, had standing to bring the case. For now, the decision of the lower courts to stop implementation of the funding cutoff is in effect. There is a split in the Circuit Courts on the issue, however, making it likely that the Supreme Court will have to resolve it sooner or later.

Health care organizations have filed a number of *amicus* briefs in these and other cases involving new abortion regulations. ACOG and others filed a brief opposing a Louisiana law that requires abortion providers to have admitting privileges at a nearby facility,[7] and a brief opposing a similar Oklahoma law.[8] The Association of Pro-Life Obstetricians and Gynecologists and others filed *amicus curiae* briefs in Box II[9] and in an Alabama case involving so-called dismemberment abortion.[10]

FAST TRACK

Azar v Allina involved more than $3 billion in reimbursements, and it represented a potentially important precendent about the rights of providers and patients to comment on Medicare reimbursement changes

Medicare payments

Azar, Secretary of Health and Human Services v Allina Health Services, et al[11]

This case drew interest—and many *amicus* briefs—from health care providers, including the AMA and the AHA.[12,13] There was good reason for their interest: First, the case involved more than $3 billion in reimbursements; second, it represented a potentially important precedent about the rights of providers and patients to comment on Medicare reimbursement changes. The question involved the technical calculation of additional payments made to institutions that serve a disproportionate number of low-income patients (known as Medicare Fractions).

At stake. The issue was a statutory requirement for a 60-day public notice and comment period for rules that "change a substantive legal standard" governing the scope of benefits, eligibility, or payment for services.[14] In 2014, the Secretary of the Department of Health and Human Services (HHS) in the Obama administration posted a spreadsheet announcing Medicare fractions rates for hospitals (for 2012)—without formal notice or comment regarding the formula used. (The spreadsheet listed what each qualifying institution would receive, but it was based on a formula that, as noted, had not been subject to public notice and comment.) The AMA and AHA briefs emphasized the importance of a notice and comment period, especially when Medicare reimbursement is involved.

Final ruling. The Court held that the HHS process violated the notice and comment provision, thereby invalidating the policy underlying the so-called spreadsheet reimbursement. The decision was significant: This was a careful statutory interpretation of the 60-day notice and comment period, not the reimbursement policy itself. Presumably, had the HHS Secretary provided for sufficient notice and comment, the formula used would have met the requirements for issuing reimbursement formulas.

Key points. Hospitals will collectively receive $3 or $4 billion as a consequence of the ruling. Perhaps more importantly, the decision signals that HHS is going to have to take seriously the requirement that it publish Medicare-related reimbursement policies for the 60-day period.

CONTINUED ON PAGE 49

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Other important cases of the most recent term

A number of diverse cases ruled on by the Supreme Court are worth mentioning. The Court:

- allowed the President to move various funds from the US Department of Defense into accounts from which the money could be used to build a portion of a wall along the southern US border.[1]
- essentially killed the "citizenship question" on the census form. Technically, the Court sent the issue back to the Commerce Department for better justification for including the question (the announced reasons appeared to be pretextual).[2]
- changed, perhaps substantially, the deference that courts give to federal agencies in interpreting regulations.[3]
- upheld, in 2 cases, treaty rights of Native Americans to special treatment on Indian Lands[4,5]; the Court held that treaties ordinarily should be interpreted as the tribe understood them at the time they were signed. (These were 5 to 4 decisions; the split in the Court leaves many unanswered questions.)
- made it easier for landowners to file suit in federal court when they claim that the state has "taken" their property without just compensation.[6]
- held that a refusal of the US Patent and Trademark Office to register "immoral" or "scandalous" trademarks infringes on the First Amendment. (The petitioner sought to register "FUCT" as a trademark for a line of clothing.)[7]
- allowed an antitrust case by iPhone users against Apple to go forward. At issue: the claim that Apple monopolizes the retail market for apps by requiring buyers to obtain apps from Apple.[8]
- held that, if a drunk-driving suspect who has been taken into custody is, or becomes, unconscious, the "reasonable search" provision of the Fourth Amendment generally does not prevent a state from taking a blood specimen without a warrant. (Wisconsin had a specific "implied consent" law, by which someone receiving a driving license consents to a blood draw.[9])
- decided numerous capital punishment cases. In many ways, this term seemed to be a "capital term." Issues involved in these cases have split the Court; it is reasonable to expect that the divide will endure through upcoming terms.

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Liability under the False Claims Act

The False Claims Act (FCA) protects the federal government from fraudulent claims for payment and for shoddy goods and services. It incentivizes (by a percentage of recovery) private parties to bring cases to enforce the law.[15] (Of course, the federal government also enforces the Act.)

At stake. The FCA has been of considerable concern to the AHA, the Association of American Medical Colleges, and other health care organizations—understandably so.[16] As the AHA informed the Court in an *amicus* brief, "The prevalence of [FCA] cases has ballooned over the past three decades.... These suits disproportionately target healthcare entities.... Of the 767 new FCA cases filed in 2018, for example, 506 involved healthcare defendants."[17]

Final ruling. The Court considered an ambiguity in the statute of limitations for these actions and the Court unanimously ruled to permit an extended time in which *qui tam* actions (private actions under the law) can be filed.[18]

Key points. As long a period as 10 years can pass between the time an FCA violation occurs and an action is brought. This decision is likely to increase the number of FCA actions against health care providers because the case can be filed many years after the conduct that gave rise to the complaint.

Registering sex offenders

The Court upheld the constitutionality of the federal Sex Offender Registration and Notification Act (SORNA).[19] Sex offenders must register and periodically report, in person, to law enforcement in every state in which the offender works, studies, or resides.

At stake. The case involved the applicability of SORNA registration obligations to those

A passing: Justice John Paul Stevens

Former Justice Stevens, the longest-living and third-longest-serving Supreme Court justice, died in July 2019 at 99 years of age. He was appointed to the Court in 1975 by President Ford and served until his retirement in 2010, when he was 90. Stevens had recently published a memoir, *The Making of a Justice: Reflections on My First 94 Years.*

Stevens's judicial philosophy generally is described as having changed over the course of his 35 years of service: He was viewed as becoming more liberal. He was a justice of enduring kindness and integrity. It is possible to find people who disagree with him, but almost impossible to find anyone who disliked him. He was continuously committed to the law and justice in the United States.

convicted of sex offenses before SORNA was adopted (pre-Act offenders).[20] The court upheld registration requirements for pre-Act offenders.

Arbitration

The Court continued its practice of deciding at least one case each term that emphasizes that federal law requires that courts rather strictly enforce agreements to arbitrate (instead of to litigate) future disputes.[21] In another case, the Court ruled that there can be "class" or "joint" arbitration only if the agreement to arbitrate a dispute clearly permits such class arbitration.[22]

FAST TRACK

The Court somewhat limited the liability of pharmaceutical companies for failing to provide adequate warning about the risk that their products pose

Pharma's liability regarding product risk

The Court somewhat limited the liability of pharmaceutical companies for failing to provide adequate warning about the risk that their products pose. The case against Merck involved 500 patients who took denosumab (Fosamax) and suffered atypical femoral fractures.[23]

At stake. Because prescribing information (in which warnings are provided) must be approved by the US Food and Drug Administration (FDA), the legal test is: Would the FDA have refused to approve a change in the warning if Merck had "fully informed the FDA of the justifications for the warning" required by state law to avoid liability?[24,25] Lower-court judges (not juries) will be expected to apply this test in the future.

The doctor and the death penalty

The Court has established a rule that, when a prisoner facing capital punishment objects to a form of execution because it is too painful, he has to propose an alternative that is reasonably available. In one case,[26] a physician, an expert witness for the prisoner, did not answer some essential relative-pain questions (ie, would one procedure be more painful than another?).

At stake. The AMA filed an *amicus* brief in this case, indicating that it is unethical for physicians to participate in an execution. The brief noted that "testimony used to determine which method of execution would reduce physical suffering would constitute physician participation in capital punishment and would be unethical."[27]

The expert witness's failure to answer the question on relative pain had the unfortunate result of reducing the likelihood that the prisoner would prevail in his request for an alternative method of execution.

Analysis

Despite obvious disagreements about big issues (notably, abortion and the death penalty) the Court maintained a courteous and civil demeanor—something not always seen nowadays in other branches of government. Here are facts about the Court's term just concluded:

- The Court issued 72 merits opinions (about average).
- Only 39% of decisions were unanimous (compared with the average of 49% in recent terms).
- On the other hand, 26% of decisions were split 5 to 4 (compared with a 10% recent average).
- In those 5 to 4 decisions, Justices were in the majority as follows[28]: Justice Gorsuch, 65%; Justice Kavanaugh, 61%; Justice Thomas, 60%; Chief Justice Roberts and Justices Ginsburg and Alito, each 55%; Justice Breyer, 50%; and Justices Sotomayor and Kagan each at 45%.
- There were 57 dissenting opinions—up

from 48 in the previous term.

- What is referred to as "the liberal-conservative split" might seem more profound than it really is: "Every conservative member of the court at some point voted to form a majority with the liberal justices. And every liberal at least once left behind all of his or her usual voting partners to join the conservatives."[29]

Last, it was a year of personal health issues for the Court: Justice Ginsburg had a diagnosis of lung cancer and was absent, following surgery, in January. Of retired Justices, Sandra Day O'Connor suffers from dementia and former Justice John Paul Stevens died.

In closing

The Court has accepted approximately 50 cases for the current term, which began on October 7. The first 2 days of the term were spent on arguments about, first, whether a state can abolish the insanity defense and, second, whether nondiscrimination laws ("based on sex") prohibit discrimination based on sexual orientation or transgender status. Cases also will deal with Patient Protection and Affordable Care Act payments to providers; the Deferred Action for Childhood Arrivals, or DACA; the death penalty; and international child custody disputes. The Court will be accepting more cases for several months. It promises to be a very interesting term. ●

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Should frequency of prenatal visits be reduced for low-risk women?

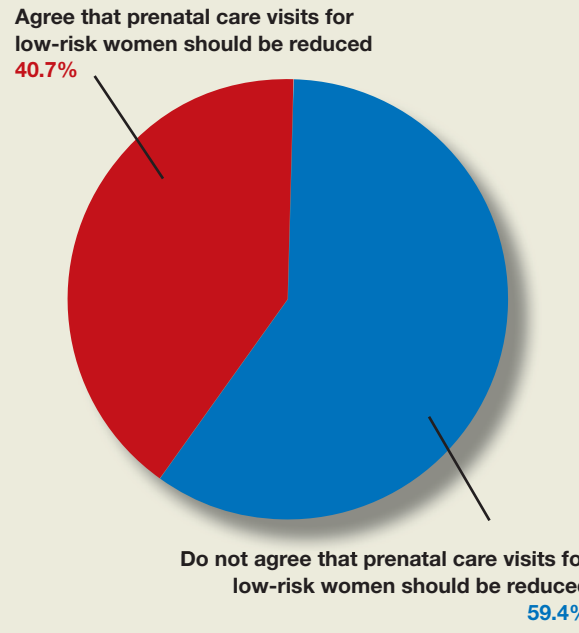
In their article, "Feasibility—and safety—of reducing the traditional 14 prenatal visits to 8 or 10" (July 2019), Erin Clark, MD, Yvonne Butler-Tobah, MD, and Lauren D. Demosthenes, MD, argued as to why a "one-size-fits-all" approach to prenatal care should be redesigned for low-risk expectant mothers. They highlighted 3 institutions that developed a reduced-visit prenatal care model incorporating remote monitoring and mobile health app technology. Women who used the reduced-visit option were overall satisfied with the technology employed and with their health care experience.

OBG MANAGEMENT polled readers with this question: "Do you agree that the number of prenatal care visits for low-risk women should be reduced?"

Poll results

A total of 123 readers cast their vote:

- **40.7% (50 readers)** said yes
- **59.4% (73 readers)** said no



PRODUCT Update

FDA REMOVES ALCOHOL BAN WITH ADDYI

Sprout Pharmaceuticals announced that the US Food and Drug Administration (FDA) has removed their contraindication on alcohol use with **Addyi**® (flibanserin). **Addyi** was approved in 2015 and is an oral nonhormonal pill for acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women. Patients are advised to discontinue drinking alcohol at least 2 hours before taking **Addyi** at bedtime or skip the **Addyi** dose that evening.

The FDA also removed the requirement, under its Risk Evaluation and Mitigation Strategy (REMS) program, for health care practitioners or pharmacies to be certified to prescribe or dispense **Addyi**. **Sprout** says that to make all labeling elements consistent with the FDA's findings the boxed warning will change and the medication guide will be updated and included under the REMS.

The most commonly reported adverse events among patients taking **Addyi** are dizziness, sleepiness, nausea, fatigue, insomnia, and dry mouth. **Addyi** is contraindicated in patients taking moderate or strong cytochrome P450 3A4 (CYP3A4) inhibitors and in those with hepatic impairment.

FOR MORE INFORMATION AND THE FULL PRESCRIBING INFORMATION AND MEDICATION GUIDE, VISIT: www.addyi.com

FEZOLINETANT FOR VMS

Astellas Pharma Inc. announced that it has initiated phase 3 trials for oral, nonhormonal **fezolinetant** to treat moderate-to-severe vasomotor symptoms (VMS) in postmenopausal women. **Fezolinetant** is a selective neurokinin-3 receptor antagonist, with dosages of 30 and 45 mg once daily being evaluated for efficacy and safety of reducing VMS frequency and severity. The trials each will enroll about 450 women with moderate-to-severe VMS at approximately 200 sites within the United States, Canada, and Europe. They will be double-blinded and placebo-controlled for the first 12 weeks, followed by non-controlled 40-week extension periods. An additional 52-week trial will investigate long-term safety.

FOR MORE INFORMATION, VISIT: http://www.clinicaltrials.gov, **TRIAL IDENTIFIERS NCT04003155, NCT04003142, AND NCT04003389**

SOLUTIONS FOR OUTCOME TRACKING

DrChrono and **OutcomeMD** announce a partnership to track and analyze patient outcome data and confounding factors. **DrChrono** is an electronic health record (EHR) system, and **OutcomeMD** is a software solution that uses literature-validated patient-reported outcome instruments to score and track a patient's symptom severity and inform treatment decisions for users.

Via a HIPAA compliant process, patients answer a list of questions that are accessed through a web link on their mobile or desktop devices. **OutcomeMD** summarizes the symptoms into a score that displays to both the physician and patient. Patients' answers and scores are pushed to the clinician's **DrChrono** EHR medical note. As care progresses in the **OutcomeMD** platform, patients remotely track how their symptoms change, and notifications alert clinicians of patients who may need attention. The integration with **DrChrono** also allows patient data on confounding factors to be automatically pushed from the patient's device into the clinician's medical note. The partnership will enable physicians to visualize patients' status, and all the factors involved in their care, on one screen, says **DrChrono** and **OutcomeMD**, strengthening documentation and saving time for both patients and clinicians. An integration demo video is available at https://youtu.be/jnh7YPII080.

FOR MORE INFORMATION, VISIT: www.outcomemd.com

NEW MATERNITY GOWN

ImageFIRST launched a new maternity gown for expecting mothers. **The Comfort Care® Maternity Gown** is a lightweight, premium polyester/nylon fabric that front snaps to allow for skin-to-skin access and optional breastfeeding. The gown also includes shoulder snaps and a full cut for extra coverage and to accommodate a variety of body types, says **ImageFIRST.**

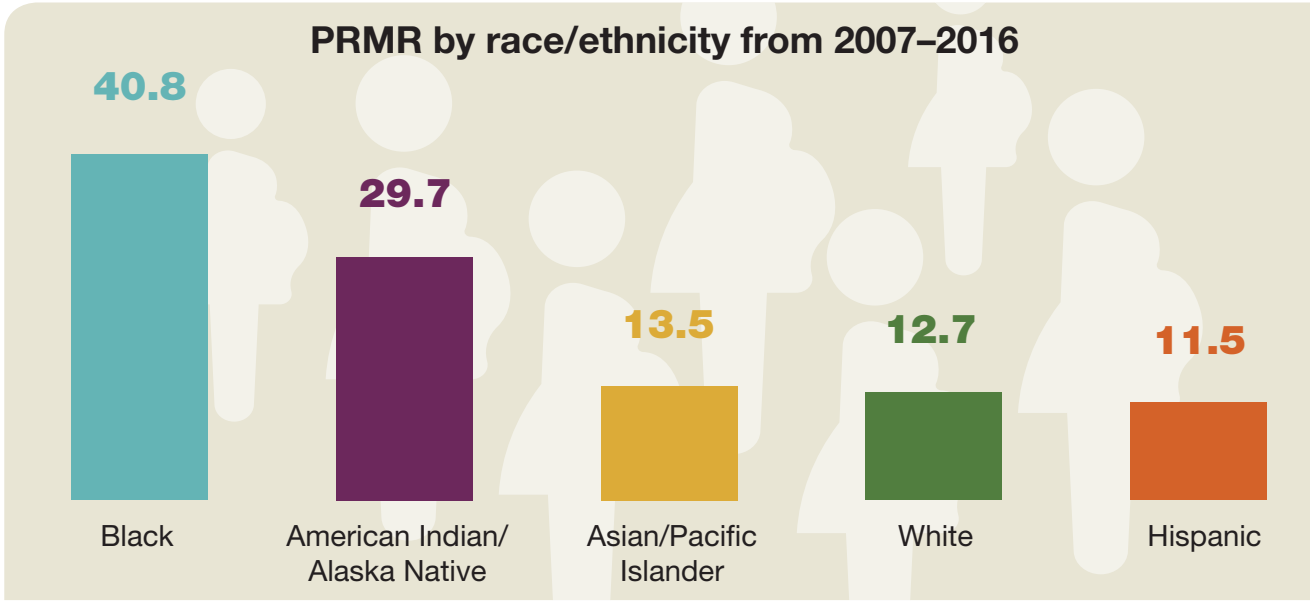
ImageFIRST is a national linen rental provider. It developed the **Comfort Care® Maternity Gown** with input from labor and delivery departments to best meet the needs of expecting mothers. It also says that a portion of the proceeds from each gown rental will be donated to the National Pediatric Cancer Foundation.

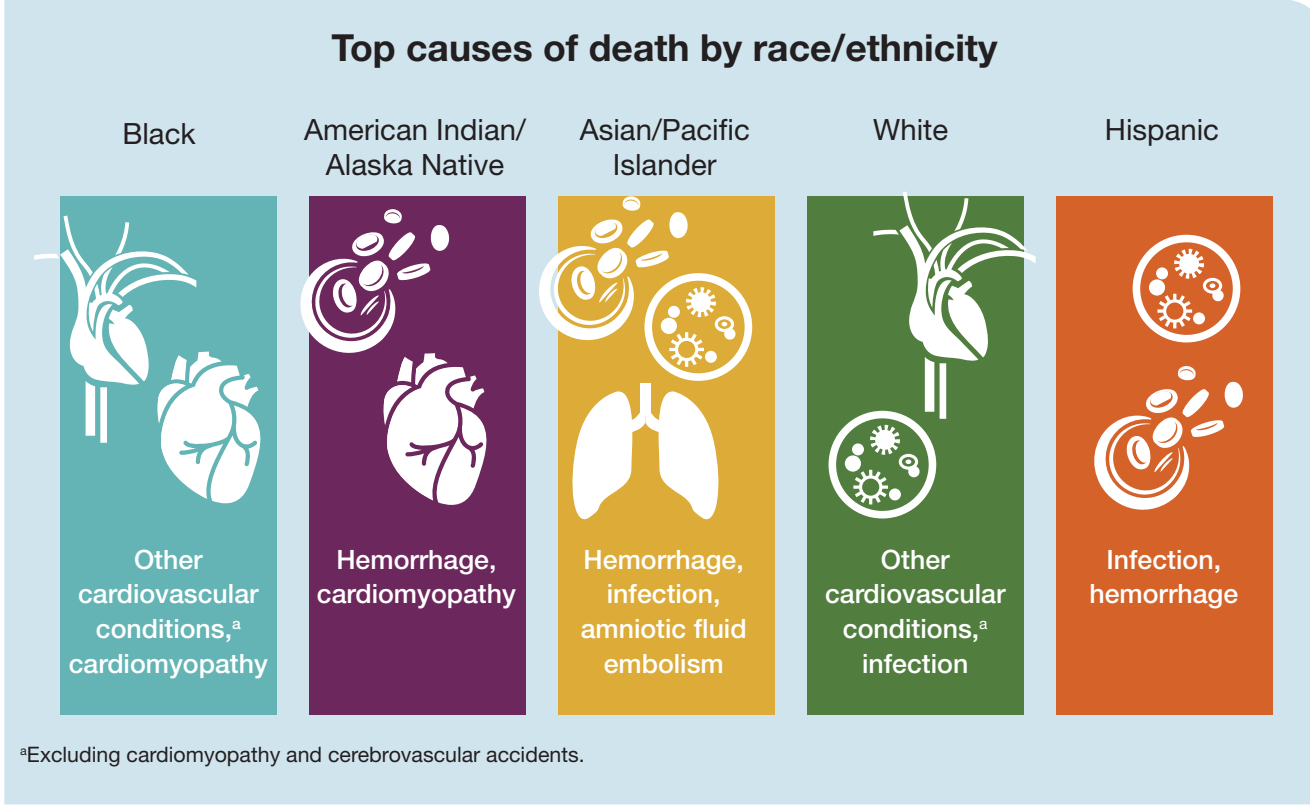
FOR MORE INFORMATION, VISIT: www.imagefirst.com

INDEX OF ADVERTISERS

Racial disparities in pregnancy-related death

The pregnancy-related mortality ratio (PRMR)—the pregnancy-related deaths per 100,000 live births—increased from 15.0 in 2007 to 17.0 in 2016; it averaged 16.7 over that timeframe (a total of 6,765 deaths). Significant disparities in pregnancy-related deaths exist. The black:white disparity in PRMR is highest among those aged 30–34 years of age.





[a]Excluding cardiomyopathy and cerebrovascular accidents.

Source: Petersen EE, Davis NL, Goodman D, et al. Racial/ethnic disparities in pregnancy-related deaths—United States, 2007–2016. *MMWR Morb Mortal Wkly Rep*. 2019;68:762-765.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Rx Only

This Brief Summary does not include all the information needed to use SOLOSEC™ safely and effectively. See full Prescribing Information for SOLOSEC.

SOLOSEC (secnidazole) 2g oral granules

Single oral dose

Initial U.S. approval: 2017

INDICATIONS AND USAGE

SOLOSEC is a nitroimidazole antimicrobial indicated for the treatment of bacterial vaginosis in adult women.

DOSAGE AND ADMINISTRATION

Administer a single 2-gram packet of granules once orally, without regard to the timing of meals. Sprinkle entire contents of packet onto yogurt, applesauce, or pudding and consume all of the mixture within 30 minutes without chewing or crunching the granules. A glass of water may be taken after the administration of SOLOSEC to aid in swallowing. SOLOSEC is not intended to be dissolved in any liquid.

CONTRAINDICATIONS

Hypersensitivity. SOLOSEC is contraindicated in patients with a history of hypersensitivity to secnidazole, other ingredients of the formulation, or other nitroimidazole derivatives.

WARNINGS AND PRECAUTIONS

Vulvovaginal Candidiasis. The use of SOLOSEC may result in vulvovaginal candidiasis and may require treatment with an antifungal agent.

Potential Risk for Carcinogenicity. Carcinogenicity has been seen in mice and rats treated chronically with nitroimidazole derivatives, which are structurally related to secnidazole. It is unclear if the positive tumor findings in lifetime rodent studies of these nitroimidazoles indicate a risk to patients taking a single dose of SOLOSEC to treat bacterial vaginosis. Avoid chronic use of SOLOSEC.

Drug Resistance. Prescribing SOLOSEC in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS

Clinical Trials Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to 589 patients, of whom 518 received a 2g dose of SOLOSEC. SOLOSEC was evaluated in 3 clinical trials of patients diagnosed with bacterial vaginosis: 2 placebo-controlled trials (Trial 1 n=215, Trial 2 n=189) and 1 uncontrolled safety trial (Trial 3 n=321).

All patients received a single oral dose of study medication or placebo. Trial 1 evaluated a 1g (this dose is not approved) dose (n=71) and a 2g dose (n=72) of SOLOSEC. Trial 2 evaluated a 2g dose (n=125). The population was female, aged 15 to 54 years. Patients in the placebo-controlled trials were primarily Black or African American (54%) or Caucasian (41%). There were no deaths in the trials. Two patients in Trial 3 discontinued due to vulvovaginal candidiasis in the SOLOSEC-treated arm.

Most Common Adverse Reactions

Among 197 patients treated with a single 2g dose of SOLOSEC in the 2 placebo-controlled trials, Trial 1 and 2, adverse reactions were reported by approximately 29% of patients. Table 1 displays the most common adverse reactions (≥2% in SOLOSEC-treated patients) in these 2 trials.

Table 1: Adverse Reactions Occurring (≥2% SOLOSEC-Treated Patients) in the Pooled Placebo-Controlled Trials 1 and 2 in Adult Women with Bacterial Vaginosis

Adverse Reaction	SOLOSEC N=197 n (%)	Placebo N=136 n (%)
Vulvovaginal candidiasis	19 (9.6)	4 (2.9)
Headache	7 (3.6)	2 (1.5)
Nausea	7 (3.6)	1 (0.7)
Diarrhea	5 (2.5)	1 (0.7)
Abdominal pain	4 (2.0)	2 (1.5)
Vulvovaginal pruritus	4 (2.0)	2 (1.5)

Among the 321 patients in an uncontrolled trial, Trial 3, adverse reactions were reported in 30% of patients. Vulvovaginal candidiasis (8.4%), nausea (5.3%), vomiting (2.5%) and dysgeusia (3.4%) were the most common adverse reactions reported in this trial.

Postmarketing Experience. The following adverse reactions have been reported during use of other formulations of secnidazole 2g outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Reported adverse reactions were nausea, dysgeusia, abdominal pain, headache, and vomiting.

DRUG INTERACTIONS

Oral Contraceptives. There was no clinically significant drug interaction between secnidazole and the combination oral contraceptive, ethinyl estradiol plus norethindrone. SOLOSEC can be co-administered with combination oral contraceptives (eg, ethinyl estradiol plus norethindrone).

USE IN SPECIFIC POPULATIONS

Pregnancy. Limited available data with SOLOSEC use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. In animal reproduction studies, there were no adverse developmental outcomes when secnidazole was administered orally to pregnant rats and rabbits during organogenesis at doses up to 4 times the clinical dose.

Lactation. Breastfeeding is not recommended. Discontinue breastfeeding for 96 hours after administration of SOLOSEC.

Pediatric Use. The safety and effectiveness of SOLOSEC in pediatric patients below the age of 18 years have not been established.

Geriatric Use. Clinical studies with secnidazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nitroimidazoles, which have similar chemical structures to secnidazole, have been associated with tumors affecting the liver, lungs, mammary, and lymphatic tissues in animals after lifetime exposures. It is unclear if these positive tumor findings in lifetime rodent studies of these nitroimidazoles indicate a risk to patients taking a single dose of secnidazole to treat bacterial vaginosis.

Secnidazole was positive in the bacterial reverse mutation assay, but was negative for the rat micronucleus test and mouse lymphoma test.

In a rat fertility study, females were dosed for 2 weeks prior to mating until Day 7 of gestation with males that were dosed for a minimum of 28 days before cohabitation. No parental toxicity or adverse effects on mating performance, estrous cycles, fertility or conception was observed at doses of up to the maximum tolerated dose (300 mg/kg/day, approximately 1.4 times the recommended dose based on AUC comparisons).

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

Manufactured for and Distributed by:
Lupin Pharmaceuticals, Inc.
Baltimore, MD 21202

Based on 7179660 Issued 10/2017

LUPIN PHARMACEUTICALS, INC.

NP-SOL-0004

A full course of BV treatment in one oral dose[1]

Solosec™ (secnidazole) is the first and only bacterial vaginosis (BV) treatment designed to deliver a complete course of therapy in just one oral dose[1,2]

To learn how Solosec may make it easy for patients to complete treatment, visit **solosechcp.com/journal.**

ONE PACKET.
ONE DOSE.
ONE TIME.

INDICATION

SOLOSEC™ (secnidazole) 2g oral granules is a 5-nitroimidazole antimicrobial agent indicated for the treatment of bacterial vaginosis in adult women.

SELECT IMPORTANT SAFETY INFORMATION

- SOLOSEC is contraindicated in patients with a history of hypersensitivity to secnidazole, other ingredients of the formulation, or other nitroimidazole derivatives.
- Vulvo-vaginal candidiasis may develop with SOLOSEC and require treatment with an antifungal agent.
- Potential risk of carcinogenicity in patients taking single-dose of SOLOSEC to treat bacterial vaginosis is unclear. Chronic use should be avoided.
- SOLOSEC is a single-dose therapy for oral use. The entire contents of SOLOSEC packet should be sprinkled onto applesauce, yogurt or pudding and consumed once within 30 minutes without chewing or crunching the granules. SOLOSEC is not intended to be dissolved in any liquid.
- In clinical studies, the most common adverse events occurring in (≥2%) of patients receiving SOLOSEC 2g oral granules were vulvovaginal candidiasis (9.6%), headache (3.6%), nausea (3.6%), dysgeusia (3.4%), vomiting (2.5%), diarrhea (2.5%), abdominal pain (2.0%), and vulvovaginal pruritus (2.0%).

Please see Brief Summary of Prescribing Information on adjacent page.

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-844-SOLOSEC (1-844-765-6732) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References: 1. SOLOSEC [prescribing information]. Baltimore, MD: Lupin Pharmaceuticals, Inc; 2017.
2. Broumas AG, Basara LA. Potential patient preference for 3-day treatment of bacterial vaginosis: responses to new suppository form of clindamycin. *Adv Ther*. 2000;17(3):159-166

PP-SOL-0096

solosec™
secnidazole
2g Oral Granules